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Pain Relief for Neonatal Circumcision – A Systematic Review

by

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Abstract

Today there are multiple research studies that address questions of interest to nursing. Would-be users of this complex and abundant research literature require valid, reliable and efficient methods for synthesis of the available evidence to determine its usefulness for nursing practice.

In this work, research synthesis, a contemporary approach to "putting together" the results of multiple primary studies of the same question, was used to examine the effectiveness and safety of pain interventions for male neonatal circumcision. Simultaneously, its usefulness for the advancement of nursing knowledge was evaluated.

Thirty-five randomized controlled trials of interventions for pain during circumcision, involving 1997 newborn infants, were included in a systematic review. The interventions tested in the primary studies include penile blocks, topical anaesthetics, oral analgesics, oral sucrose, and environmental manipulation. Active interventions were compared with placebo, no treatment, or another active intervention in 16 different comparisons. The outcome of interest was pain as assessed by physiological, biochemical, or cry variables, or by validated pain measures.

Dorsal penile nerve block (DPNB) was identified as the most effective intervention for reducing neonatal pain responses during circumcision. Ring block and eutectic mixture of local anaesthetics (EMLA) were also effective in reducing pain responses, but to a lesser degree than DPNB. Oral sucrose, oral analgesics, and environmental manipulation were not effective for pain. Adverse effects associated with the interventions were infrequent and not considered serious. Recommendations for best practice for circumcision pain management and for future research were developed.

This thesis includes four manuscripts. The first consists of an overview that provides the rationale for the research, and the second discusses the use of synthesis methods for the advancement of nursing knowledge. Two manuscripts present the findings of the research. One includes the findings of the systematic review in their entirety and one is an abridged version that highlights results for the most frequently evaluated pain outcomes, heart rate and cry behaviour, and focuses on clinical implications. A concluding chapter includes recommendations for practice and future research.

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CHAPTER ONE

Overview of the Dissertation

The purpose of my dissertation research was twofold. The first was to assess the utility of research synthesis for advancing nursing knowledge. The second was to employ synthesis methods to examine the effectiveness and safety of pain relief interventions for male neonatal circumcision. Synthesis of this body of research was specifically chosen as the topic because pain assessment and management are critically important nursing responsibilities, and evidence for best practice is needed to assist nurses to provide effective care. At the same time, conduct of the systematic review enabled evaluation of the potential for synthesis to advance knowledge for nursing practice in neonatal pain management and in other areas where multiple studies of the same question exist.

The findings of the systematic review are presented here using a mixed paper format, an option that is accepted by the Faculty of Graduate Studies and Research of the University of Alberta. The complete dissertation is comprised of an introductory chapter which presents the background for the research, three manuscripts, and a final discussion paper that includes recommendations for practice and future research.

With exception of the introductory section, the chapters contained in this document represent a series of publishable manuscripts, each intended for a specific journal and audience. For that reason, similar content appears in several of the manuscripts. The manuscripts, including the references, are prepared in the style appropriate for the chosen journal.

Background

Circumcision is the most common surgery performed on otherwise healthy males during the newborn period. Regional rates of circumcision vary somewhat across the United States (US), for example, 81% in the Midwest (Quayle, Coplen, & Austin, 2003) and 37% in the state of Washington (Christakis et al., 2000). Overall, approximately 1.2 million newborn males are circumcised annually in the US at a cost of 150 to 270 million dollars (American Academy of Pediatrics [AAP], 1999). In Canada, it is estimated that 48% of male neonates are circumcised (Canadian Pediatric Society [CPS], 1996), although like the US, circumcision rates vary across the provinces. De-listing of the procedure from Medicare coverage in most Canadian provinces makes it difficult to obtain up to date, accurate rate data.

Circumcision is not just a North American phenomenon; the surgery is considered routine or part of tradition in many places in the world. And, over time, immigration can influence circumcision rates in other places, when immigrants carry traditions to their new homes. Circumcision is performed around the world for religious reasons in keeping with Jewish and Islamic faiths (Szasz, 1996). In Ethiopia, routine circumcision of males is mandated by traditional beliefs (Asefa, Hewison, & Drewett, 1998; Hodes, 1997). Circumcision is regarded in Turkey as a right of passage necessary to establish masculine identity though it is not always performed during the neonatal period (Sahin, Beyazova, & Akturk, 2003). Recently, circumcision rates have increased dramatically in some countries such as Korea where it is estimated that 60% of all males are now circumcised (Oh et al., 2002; Pang & Kim, 2002).

Risks of Circumcision

Circumcision carries risks. These include bleeding, amputation of the glans, acute renal failure, sepsis and rarely, death (AAP, 1999; CPS, 1996). On the other hand, circumcision may confer some health benefits. Research has shown that the surgery protects against urinary tract infection (UTIs) in infants, and penile cancer and sexually transmitted diseases (STDs) in adults (Schoen, 2003). The significance of this evidence is controversial and the current consensus of medical opinion is that the low incidence of UTIs and adult penile cancer diminishes the relevance of the potential medical benefits of routine circumcision in comparison to the risks of the surgery. Moreover, behaviour is thought to be a more important factor in the prevention of STDs than circumcision status. The CPS (1996), the AAP (1999), the American Medical Association [AMA] (2005), and the American College of Obstetricians and Gynecologists [ACOG] (2001) no longer recommend that circumcision of male neonates be performed routinely.

Parental Decision-Making about Circumcision

Parents make the decision as to whether their child will be electively circumcised. It is interesting to note that these decisions are not strongly influenced by information about the medical benefits or disadvantages of the surgery (Bauchner, 2003; Binner, Mastrobattista, Day, Swaim, & Monga, 2002; Maisels, Hayes, & Conrad, 1983), or by availability of healthcare coverage for the procedure (Quayle, Coplen, & Austin, 2003; Walton, Ostbye, & Campbell, 1997). Instead, cultural norms appear to exert considerable influence when circumcision is viewed as something "good parents do" (Waldeck, 2003). In spite of this, the moral acceptability of parental consent for circumcision of an incompetent (i.e. unable to consent) newborn has become a subject of debate in the professional literature. In a recent paper on the ethics of male neonatal circumcision, Benatar and Benatar (2003) concluded that as the procedure constitutes "neither a compelling prophylactic measure, nor a form of child abuse" (p 45), non-therapeutic circumcision falls within the mandate of parental decision-making. Others disagree vehemently (Antommeria, 2003; Hill, 2003) and cite legal considerations and the rights of the child (Davis, 2001; Van Howe, Svoboda, Dwyer, & Price, 1999). The impact ethical and legal perspectives will have on future parental decision-making about circumcision remains to be seen.

The AAP, CPS, ACOG, AMA all agree that anaesthesia should be used to prevent or reduce pain during circumcision surgery. A variety of circumcision pain interventions have been tested including penile blocks, topical anaesthetics, oral analgesics, oral sucrose, and environmental manipulation. Nonetheless, the majority of infants still undergo the surgery without analgesia or anaesthesia (Myron & Macquire, 1991; Ryan & Finer, 1994; Snellman & Stang, 1995; Wellington & Rieder, 1993). In one study, only 71% of pediatricians, 56% of family practitioners, and 25% of obstetricians reported use of pain interventions for circumcision in part because of concerns about adverse drug effects (Stang & Snellman, 1998). Others cite lack of familiarity with pain management techniques (Wellington & Rieder, 1993). Evidently, many physicians do not receive training in management of circumcision pain (Howard, Howard, Garfunkel, Blieck, & Weitzman, 1998).

Possibly because they normally are not encouraged to, or choose not to observe the circumcision surgery, parents have not actively advocated for adequate management of circumcision pain (Smith & Smith, 2000). They are often un-informed, misinformed or confused by conflicting and incomplete information about the surgery and about alternatives for pain management (Mau, Holland, & Yamamoto, 2004; Okino & Yamamoto, 2004). In addition, the strength of the cultural norms and entrenched beliefs about masculinity and pain tolerance may prevent parents from objectively evaluating all of the issues and they may discount the degree of pain and trauma experienced by the child during circumcision (Waldeck, 2003). In the following sections, neonatal nociceptive capabilities and responses during un-anesthetised circumcision are discussed.

Neonatal Nociceptive Capabilities and Pain Responses

The neuroanatomic apparatus for conducting nociceptive (pain) impulses from the periphery to the sensory cortex is intact in the neonate (AAP & CPS, 2000; Anand & Carr, 1989; Anand & Hickey, 1987). The density of nociceptive nerve endings is similar to adult levels and the development of cells in dorsal horn is complete by 30 weeks gestation (Anand, 1990). Incomplete myelination of neonatal nerve fibres implies slower conduction of noxious impulses, however, this effect is offset by shorter interneuron distances traveled in the newborn (Anand & Hickey, 1987; Fitzgerald & Anand, 1993). The cortex has a complete complement of neurons by 20 weeks (Anand & Hickey, 1987), and complete myelination of nerve tracts in the spinal cord and central nervous system is achieved by 30 weeks gestation. Functional maturity of the cortex is suggested by studies of cerebral metabolism, the results of electroencephalograms and by evidence of establishment of distinctive sleep-wake cycles by 28 weeks gestation. Further development of neural structures and pathways during infancy and early childhood serves to refine the functional and complex neonatal nociceptive system (Anand, 1990; Anand & Hickey, 1987; Fitzgerald & Anand, 1993).

Nociceptive inputs to the central nervous system can have widely variable effects on physiological systems and processes including the immune, endocrine, and cardiovascular systems (Fitzgerald & Anand, 1993). Newborns exhibit a relatively greater magnitude of response to stress and a lower threshold to noxious stimuli, and may perceive pain more intensely than older children or adults because descending control mechanisms are immature and less endogenous modulation of noxious stimuli is possible (Anand, 2001; Fitzgerald & Anand, 1993). In neonates, unrelieved pain resulting from nociceptive stimuli can trigger sympathetic nervous system stress responses and affect other major body systems with potentially life-threatening results.

Sympathetic activation during and after noxious stimuli is associated with increased secretion of pituitary, adrenal and pancreatic hormones in response to stress and hypermetabolic states which may disturb normal metabolism and exert detrimental cardiovascular effects (Anand & Carr, 1989). Disruptions of metabolism may have critical consequences because metabolic stability is inherently more difficult to sustain in the neonate due to the need to maintain body temperature and somatic growth within a narrow range, the smaller protein, fat and carbohydrate reserves, and the transient immaturity of neonatal enzyme systems (Anand & Carr, 1989; Anand & Hickey, 1987).

Pain experienced early in life may lead to exaggerated affective or behavioural responses during subsequent pain events. Male infants who were subjected to unanesthetized circumcision in the neonatal period showed increased behavioural responses to routine vaccination at several months of age (Taddio, Katz, Ilersich, & Koren, 1997a). Preterm infants who experienced several weeks of neonatal intensive care (NICU) exhibited diminished behavioural responses and increased cardiovascular responses in response to heel stick when compared to an "inexperienced group" of the same post-conceptual age. The differences in their behavioural responses were strongly correlated with the number of invasive procedures experienced since birth, suggesting that repetitive noxious stimuli may lead to subsequent altered responses in preterm neonates (Anand, 1998; Johnston & Stevens, 1996). Similar results were obtained in another study in which facial expression, state, and heart rate variability were evaluated in 136 infants at 32 weeks post-conceptual age undergoing heel lance. The number of invasive procedures since birth and gestational age at birth were the most significant factors associated with dampened behavioural and autonomic responses, while previous exposure to morphine was associated with normalized responses (Grunau, Oberlander, Whitfield, Fitzgerald, & Lee, 2001). Excessive excitatory activation caused by repetitive noxious stimuli may damage developing neurons and increase the risk of behavioural problems such as anxiety, altered pain sensitivity, hyperactivity and stress disorders for infants born preterm (Anand & Scalzo, 2000).

Measurement of Neonatal Pain

Pain is a construct that cannot be measured directly. Instead, pain is inferred from observations that are assumed to be correlated with the experience of pain. In older children and adults, self-report is considered to be the gold standard for pain assessment, but their inability to talk rules out use of self-report for neonates. While behavioural and physiological indicators can be considered a special type of neonatal "self-report" for neonates and non-verbal infants, their expression is dependent on gestational age, state, degree of illness, and other factors such as habituation which can occur with repetitive noxious stimuli. In addition, neonates tend to exhibit stereotypic behavioural responses to a variety of stimuli, and thus behaviour alone cannot be used to distinguish between pain and distress. Accordingly, multidimensional pain measures are generally recommended to promote accurate measurement of neonatal pain (Abu-Saad, Bours, Stevens, & Hamers, 1998; Franck & Miaskowski, 1997; Stevens, 1999).

Generally three classes of indicators are used to quantify neonatal pain. Because pain is a significant stressor, hormones associated with the stress response are released during painful experiences. Thus, biochemical indicators represent the most direct reflection of the stress response. Hormones of the hypothalamic-pituitary-adrenal axis including salivary and serum cortisol are the most frequently measured biochemical indicators. These indicators are non-specific for pain as cortisol levels do increase in response to crying, circumcision, heel stick, and surgery, but also in response to some non-painful stimuli (Franck & Miaskowski, 1997).

Physiologic indicators include heart rate, respiratory rate, blood pressure, transcutaneous oxygen saturation (TcPO$_2$), transcutaneous carbon dioxide (TcCO$_2$), oxygen saturation (SaO$_2$), palmar sweat, intracranial pressure (ICP) and vagal tone. Heart rate is by far the most frequently evaluated physiologic indicator and the responses to stimuli are bi-directional. Visual and auditory stimuli cause brief, small decreases in heart rate, while strong stimuli or emotional responses lead to significant increases in heart rate. Heart rate increases with noxious stimuli, and remains elevated for a period of time after the stimulus is removed (Sweet & McGrath, 1998). Heart rate is widely used as a pain indicator and is simple to record, but its lack of specificity to noxious stimuli makes an inadequate stand alone measure of pain.

Behavioural indicators of pain include facial expression, cry, gross motor movement, and changes in state. Immediate reactions to noxious stimuli are withdrawal, grimacing and crying, although some infants do not cry when subjected to noxious stimulation. Facial expression of pain is the most comprehensively studied behavioural indicator. A frequently utilized measure, the Neonatal Facial Coding System (NFCS), relies on a single behavioural indicator, facial action, to assess pain response (Grunau & Craig, 1987).

Multidimensional pain measures have been developed that use more than one indicator for assessment. Generally these measures combine physiological and behavioural indicators, and occasionally add contextual indicators, to develop an overall pain score. Multidimensional measures such as the Neonatal Infant Pain Scale (NIPS) (Lawrence et al., 1993) and the Premature Infant Pain Profile (PIPP) (Stevens, Johnston, Petryshen, & Taddio, 1996) are frequently utilized for assessment of acute procedural pain in term and preterm neonates.

Factors that Influence Pain Responses in Neonates

Neonatal pain responses can be influenced by several factors including gestational age, gender, state, severity of illness and previous pain experiences (Anand, 2000). The most significant factors associated with behavioral and autonomic pain reactivity at 32 weeks post-conceptual age are gestational age at birth and number of invasive procedures since birth (Grunau et al., 2001). In a study of preterm infants undergoing heel lance, infants born at 25 – 27 weeks gestation reacted to an invasive procedure. Younger gestational age was associated with less facial activity and diminished robustness of response; the magnitude of response was greater in more mature infants (Craig, Whitfield, Grunau, Linton, & Hadjistavropoulos, 1993). Behavioural state in turn influences facial pain expression. Infants in sleep states exhibit less facial activity after heel lance when compared with infants in awake-alert states (Stevens, Johnston, & Horton, 1994).

Differences in pain perception may be attributable to gender. In one study, newborn female neonates of all gestational ages exhibited more facial actions associated with pain than male infants during blood sampling and one minute afterwards (Guinsburg et al., 2000).

Severity of illness also affects the expression of pain, especially cry responses. In a study of 124 premature infants, Stevens et al. (1994) found that sick infants exhibited shorter cry duration and higher pitched cry during the most invasive stage (stick) of a heel lance procedure.

Pain Responses during Un-anesthetised Circumcision

Traumatic conditions, such as surgery without anaesthetic, activate the pituitary-adrenal cortical system. Gunnar, Fisch, Korsvik, and Donhowe (1981) examined behavioural state and serum cortisol levels in eight healthy neonates undergoing unanesthetized circumcision 57 – 80 hr after birth and found that post-surgical cortisol levels were three to four times baseline levels. In this trial, the amount of crying returned to pre-circumcision levels rapidly, as the infants were fed and comforted post-circumcision by their mothers. In another study, statistically significant increases in cortisol levels were observed in five healthy neonates following circumcision performed during the first six hours of extrauterine life (Talbert, Kraybill, & Potter, 1976).

Besides biochemical responses, cry, changes in oxygen levels and sleep-wake state can be a sign of pain in infants. Healthy male infants 48 to 72 hours of age had significant decreases in transcutaneous oxygen levels ($tcPO_2$) during unanesthetized circumcision although they rebounded quickly in the post-operative period. In addition, average heart rate and respiratory rate were higher during and after circumcision compared to pre-surgical levels (Rawlings, Miller, & Engel, 1980).

The effect of circumcision on sleep-wake state was assessed in eleven healthy, three day-old neonates. These neonates did not sleep as a way of recovering from pain of unanesthetized circumcision. Instead, total wakefulness (characterized by fussy-crying) increased significantly immediately following the procedure (Anders & Chalemian, 1974). During unanesthetized circumcision, cries are of the greatest urgency during the most invasive phase of the surgery (Porter, Miller, & Marshall, 1986). Crying patterns return to pre-circumcision levels within 10 minutes after the surgery.

The results of these studies demonstrate that unanesthetized circumcision is associated with negative physiological, biochemical and behavioural responses. Unanesthetized circumcision has also been linked with complications such as apnea and choking (Lander, Brady-Fryer, Metcalfe, Nazarali, & Muttitt, 1997), gastric rupture (Connelly, Shropshire, & Salzberg, 1992), and recurrence of pneumothorax (Auerbach & Scanlon, 1978). Infants circumcised without anaesthesia exhibit stronger pain responses to routine immunizations during the first six months of life compared with infants who were not circumcised (Taddio et al., 1997) suggesting that circumcision pain may exert long-term effects on infant behaviour. Interventions intended to prevent or reduce these adverse outcomes are discussed in the next section.

Interventions for Circumcision Pain

Discrete aspects of the system for nociceptive processing are targeted by various approaches to the prevention and management of pain. Pharmacological interventions generally act to inhibit the transmission of noxious impulses or to decrease the production of pain producing substances in the body tissues. Non-pharmacological interventions encompass physical, behavioural or cognitive techniques designed to modify contextual factors associated with pain or individual sensory systems, behaviours or ability to cope with pain (McGrath, 1990).

Topical anaesthetics. Topical anaesthetics are applied to intact skin or mucous membrane and provide anaesthesia without the need for invasive injections. Percutaneous absorption of these medications is affected by the thickness of the epidermis and the hydration of the skin. The normal structure of neonatal skin promotes the absorption of transdermal preparations, but also increases the risk of toxicity associated with inappropriate dose regimens (Koren & Jacobsen, 1993). The topical anaesthetic *eutectic mixture of local anaesthetics* (EMLA) is a water-based cream that is 2.5% lidocaine and 2.5% prilocaine. EMLA is frequently recommended for treatment of acute procedural pain. The combination of drugs in the cream melts at a low temperature, which permits a higher effective surface concentration and enhances the rate of uptake (Stevens, 1999). For adequate absorption, the cream must be applied for at least 60 minutes prior to the procedure and be covered with an occlusive dressing (Wilder, 2000). Local skin reactions have been reported with the use of EMLA cream, including blanching, erythema, and edema of the skin at the site of application, but these are usually transient and are generally not considered serious (Koren, 1993).

Methemoglobinemia (MetHb), caused by oxidation of hemoglobin by the metabolites of prilocaine is a serious but relatively rare risk associated with EMLA use in neonates that has led to avoidance of the use of EMLA for procedural pain in infants less than 12 months of age. A recent systematic review of the use of EMLA for acute procedural pain demonstrated that the risk of significant MetHb (defined as MetHb > 5% and clinical signs such as cyanosis requiring treatment) is low with single dose applications of 0.5 to 2 g applied for 10 – 180 minutes for fullterm neonates, and 0.5 to 1.25 g applied for 3 - 180 minutes for preterm neonates (Taddio, Ohlsson, Einarson, Stevens, & Koren, 1998).

EMLA has been tested for effectiveness for preventing circumcision pain. When compared with placebo, newborn term infants that received EMLA prior to circumcision had significantly lower heart rates (average of 25 beats per minute less), 5% higher oxygen saturations, 20% less facial activity and 15% less crying during various steps of the circumcision procedure (Benini, Johnston, Faucher, & Aranda, 1993). Taddio et al. (1997b) also observed less facial activity, time crying, and lower heart rates in newborns that received EMLA prior to surgery compared to those who received placebo.

The technique for administration of EMLA and other topical anaesthetics presents some difficulties in application for circumcision. Considerable skill is required to apply the cream on and around the penis, and to place the occlusive dressing that covers the cream to keep it in place. The medication must be reapplied if the infant voids during the application wait time. These technical challenges along with the considerable wait time prior to surgery may limit the feasibility of topical anaesthetics for circumcision in some settings.

Oral sucrose. Sucrose or other sugar solutions alone or in combination with non-nutritive sucking have been examined as interventions for procedural pain management (Mitchell, Brooks, & Roane, 2000). Oral sucrose is thought to activate central endogenous pathways, and may stimulate release of endorphins from the hypothalamus. The analgesic effect of sucrose is activated within two minutes, and lasts for three to five minutes (Haouari, Wood, Griffiths, & Levene, 1999; Mitchell & Waltman, 2003).

Like sucrose, non-nutritive sucking is frequently used as a management strategy for procedural pain in neonates (Franck & Miaskowski, 1987). Non-nutritive sucking (NNS) is thought to have an analgesic-like effect through stimulation of orotactile and mechanoreceptor mechanisms (Gibbons & Stevens, 2001; Mitchell & Waltman, 2003). The sensations created by non-nutritive sucking may deflect attention away from the noxious stimulus and facilitate self-regulation because the infant can control the sucking. Sucrose and non-nutritive sucking may operate synergistically when offered in combination, and provide more effective pain relief (Carbajal, Chauvet, Coudere, & Olivier-Martin, 1999; Gibbons & Stevens, 2001; Gibbons et al., 2002).

Although sucrose in a wide variety of dosages (concentrations from 12 to 24%, and volumes from 0.05 to 2.0 ml) has generally been found to decrease acute, procedural pain responses in neonates (Mitchell et al., 2000; Stevens, Taddio, Ohlsson, & Einerson, 1997), the optimal dose has not yet been identified. A recent systematic review and meta-analysis of three studies indicated that a 0.12 g dose is effective to reduce responses to procedural pain in term infants. Higher doses do not appear to increase effectiveness (Stevens, Yamada, & Ohlsson, 2004). In comparison, relatively small doses of sucrose (e.g. 0.01 to 0.02 g) appear to be effective for preterm infants (Johnston, Stremler, Stevens, & Horton, 1997).

Interest in sucrose or other sugar solutions used alone or combined with other interventions such as non-nutritive sucking for circumcision pain is reflected in the design of recent circumcision research although the results obtained appear to be inconsistent. Infants who were given a concentrated (50%) dextrose solution before circumcision did not have significant differences in heart rate, oxygen saturation, or time crying when compared with infants who received water placebo (Kass & Holman, 2001). In a different study, the infants who received 24% sucrose had a cumulative mean time crying of 56 seconds when compared with the placebo group time of 86 seconds (Kaufman, Cimo, Miller, & Blass, 2002).

Penile blocks. The use of dorsal penile nerve block (DPNB) for neonatal circumcision was first described by Kirya and Werthman in 1978. While 1% lidocaine is generally used for the block, 0.25% bupivacaine without epinephrine is also recommended (Wilder, 2000). A recent meta-analyses of selected outcomes of two trials in which DPNB was compared with no treatment or a control group indicated a significant reduction in time crying [WMD -52.9%, 95% CI -65.9 to -40] and smaller changes in oxygen saturation in the DPNB group compared to control [WMD -1.1%, 95% CI -1.8 to -0.40], but no difference in plasma cortisol levels 30–40 minutes post-surgery (Taddio, 2001).

Ring block (RB), established by subcutaneous, circumferential infiltration of 1% lidocaine around the shaft of the penis near the base, was first described as a method for post-circumcision analgesia (Broadman et al., 1987), but has since been examined as an intervention for pain during circumcision. When compared with EMLA and DPNB, infants treated with RB had smaller increases in heart rate during the foreskin separation stage of the circumcision procedure (Lander et al., 1997). In another trial, infants receiving RB cried 36% less than no treatment controls (p <.005), and had smaller increases in heart rate during all stages of circumcision (p <.005) (Hardwick-Smith, Mastrobattista, Wallace, & Ritchey, 1998).

Ring block and local block anaesthesia as described by Masciello (1990) may have a lower risk of complications compared to DPNB because the anaesthetic is injected away from the major vessels decreasing the likelihood of bleeding or intravascular injection of the lidocaine (Myron & Maguire, 1991). A five-minute waiting period after anaesthetic infiltration is recommended for both DPNB and RB to achieve maximum effectiveness of the block.

The use of buffered lidocaine to reduce the pain associated with injection of anaesthetics to achieve penile blocks has been examined as a strategy to promote overall comfort during all phases of the circumcision procedure. In a trial of this intervention there were no significant differences in heart rate, oxygen saturation, and behavioural state (Newton, Mulnix, Baer, & Bovee, 1999; Stang et al. (1997) between buffered lidocaine and regular lidocaine groups.

Oral analgesics. Acetaminophen is the most frequently prescribed non-opioid oral analgesic used to treat mild to moderate pain in pediatric populations (Berde & Sethna, 2002; McGrath, 1990). It is safe and effective for neonates and can be administered orally or rectally (Stevens, 1999). Oral acetaminophen has been evaluated as an intervention for circumcision pain in several trials. In one, acetaminophen did not reduce heart rate, respiratory rate, or crying when compared with placebo (Howard, Howard, & Weitzman, 1994). Another trial also found no significant differences between acetaminophen and placebo groups in crying and heart rate, however, acetaminophen did appear to have a positive effect on post-circumcision mother-infant feeding interactions (Macke, 2001).

Surgical clamps. The relative efficacy of surgical devices or clamps used for the circumcision surgery (i.e. the Mogen and Gomco clamps), alone or in combination with other pain interventions, has been compared in several trials. The particular device used may effect the overall time required to do the surgery and in turn reduce the total amount of pain experienced (Taeusch et al., 2002).

Non-pharmacological interventions. The use of non-pharmacological techniques to prevent or reduce pain is based on the premise that modifying environmental or internal factors through physical, behavioral, or cognitive strategies influences the transmission, perception and modulation of noxious impulses and attenuates neuronal impulses from noxious stimuli. Non-pharmacological interventions can be administered alone or in combination with pharmacological measures to reduce pain, decrease stress, and provide comfort. In trials of music, intrauterine sounds, pacifiers, and combinations of these as pain interventions, no differences were found between treatment and control groups (Marchette, Main, & Redick, 1989; Marchette, Main, Redick, Bagg, & Leatherland, 1991). Infants restrained in a specially designed chair during the surgery demonstrated a 50% reduction in their behavioral distress scores compared with the control group that was positioned using traditional methods (Stang et al., 1997).

Rationale for the Research

Sufficient evidence exists that neonates experience and are negatively affected by untreated pain. Neonatal responses to acute procedural pain associated with circumcision have been examined, and a number of interventions for circumcision pain have been identified. Although each of these interventions has been evaluated in at least one clinical trial, little attempt has been made to systematically combine the results from several different trials of the same intervention, or to compare their relative effectiveness and safety for circumcision pain. The resultant lack of consensus on best practice, despite significant research effort, means that effective pain management during circumcision is not always implemented.

Nurses are accountable to provide effective pain assessment and management. This is especially important when nurses are caring for vulnerable, non-verbal patients. This body of research posed a unique opportunity to simultaneously assess the utility of synthesis for generating knowledge for nursing (e.g. knowledge about management of neonatal pain), and to resolve the uncertainty about best practice for circumcision pain management. I reasoned that synthesis of the evidence gained to date in this area was important to develop and refine the theory and knowledge needed as an aid to professional decision-making, because circumcision is an area where nurses play a variety of roles. Furthermore, I believe that synthesis of the evidence will facilitate increased awareness of the need for appropriate pain management for all invasive procedures performed in the neonatal period, and help to ensure that future research efforts in this area are productive.

Overview of the Research

Objectives of the Research

Objective 1: To assess the usefulness of synthesis methods for advancing nursing knowledge.

Objective 2: To conduct a systematic review to assess the effectiveness and safety of interventions for relief of pain during circumcision.

Objective 3: To develop evidence-based recommendations for best practice in circumcision pain management, and to identify areas where further research is needed.

Summary of the Methods

My dissertation research was designed as a systematic review of the individual and relative effectiveness and safety of interventions for relief of circumcision pain. The research followed the guidelines set out by the Cochrane Collaboration in the Cochrane Reviewers' Handbook (Alderson, Green, & Higgins, 2003). Founded in 1993, the Cochrane Collaboration is an international, independent, non-profit organization dedicated to making current, accurate information about the effects of healthcare available worldwide. The primary activity of the Cochrane Collaboration is the production and dissemination of systematic reviews of healthcare interventions, and the volunteer reviewers are recognized worldwide for their expertise in this regard. Editorial teams associated with the Cochrane Entities (Steering Group, Review Groups, Centres, Methods Groups, etc.) oversee the preparation of the reviews and assist reviewers to ensure that quality standards are met. Research protocols and completed reviews are published quarterly in the *Cochrane Database of Systematic Reviews* as part of the Cochrane Library.

The steps involved in a systematic review of quantitative research include a priori development of an explicit research protocol that clearly outlines the research question and the procedures for identifying eligible studies with relevant data. The protocol guides the research, ensures that the procedures and methods used can be replicated, and reduce the potential for bias and threats to the validity of the review. In the first phase of this research, a detailed protocol outlining procedures for the review was submitted to and approved by the Cochrane Neonatal Review Group including J. Sinclair, J. Horbar, M. Bracken, and R. Soll. A copy of the protocol, which has been published in the Cochrane Library, is included here as Appendix A.

Trials involving male term or preterm infants undergoing circumcision during the neonatal period were the "subjects" of the research. Randomized controlled trials (RCTs) of any type of intervention intended to relieve pain during circumcision were included in the study sample, and a comprehensive search of the existing research literature was undertaken to identify relevant studies. Thirty-five RCTs that compared pain interventions with placebo or no treatment, or compared two active interventions for pain during circumcision were included in the review. In total, 1997 newborns were involved in the included studies.

The primary outcome chosen for evaluation of the effectiveness of the interventions was pain as assessed by physiological, biochemical, behavioral, or cry variables. Secondary outcomes assessed included complications of pain interventions and difficulties in implementation of pain interventions as reported by researchers. Data (e.g. the outcome data included in the trial reports) were analyzed using the statistical package

(RevMan 4.2) provided by the Cochrane Collaboration. The methods employed for the research are described in detail in Manuscript Two.

Guidelines and recommendations for practice and recommendations for future research based on the results of this review are presented and discussed in several of the manuscripts.

Summary of the Manuscripts

Manuscript One. The first manuscript is written for *Journal of Advanced Nursing*. The manuscript describes the aims and basic procedures of quantitative research synthesis as well as its limitations. The contributions of research synthesis to knowledge and theory development, evidence-based practice and research are discussed. The paper is entitled "*Research Synthesis: A Means to Advance Nursing Knowledge*".

Manuscript Two. The second manuscript, which has been published, is the completed systematic review.

Brady-Fryer, B., Wiebe, N., & Lander, J. A. (2004). Pain relief for neonatal circumcision. The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No. CD004217.pub2. DOI: 10.1002/14651858.CD004217.pub1.

Reported in this manuscript are the findings on the effectiveness and safety of the pain interventions that were tested in the included trials.

Manuscript Three. The third manuscript is an abridged version of the full systematic review entitled *Pain Interventions for Neonatal Circumcision - A Systematic Review,* has been prepared for submission to the journal *Pediatrics*. A subset of the entire findings presented in Manuscript Two, focusing on the most frequently measured outcome variables, i.e. heart rate and time crying, are addressed in the paper. The purpose of the paper is to facilitate dissemination of the research to clinical practitioners and other professionals who perform circumcision and advise parents of newborns.

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CHAPTER TWO

Research Synthesis – A Means to Advance Nursing Knowledge

In order that nursing, a practice discipline, be guided by theory and a credible body of knowledge, scientists must find a means to learn from and build on existing evidence. Today there are multiple studies that address questions of interest to nursing. Would-be users of this increasingly complex and abundant research literature require valid, reliable and efficient methods to synthesize the available empirical evidence to determine its usefulness for practice, theory development, and future research.

Traditionally, nursing, like other disciplines, has made use of narrative, that is, integrative, reviews of the literature as a way to encapsulate existing research information. A review of this type is intended to stimulate dialogue about the conclusions that have been reached in the individual studies and generate new research. At their weakest, integrative reviews are merely summaries of existing evidence. At their best, they provide an analysis of the status of a particular field and evaluate the fit of the acquired evidence to prevailing theories. Whether strong or weak, integrative reviews are original works in that each author includes a unique set of literature and/or interprets its meaning in a distinctive way. Procedures for identifying articles or determining what topics will be addressed are rarely documented and reviews of this type are unlikely to be replicated (Egger, Davey Smith, & Altman, 2001; Glass, 1976; Hunter, Schmidt, & Jackson, 1982; Thorne, Jensen, Kearney, Noblit & Sandelowski, 2004; Wolf, 1986).

Another approach for "putting together" the results of extant research is synthesis, which is the topic of this paper. The purposes of this paper are to describe the scientific process of research synthesis and to discuss its relevance for the advancement of nursing knowledge. Synthesis terminology is clarified and key synthesis procedures are presented. The role that research synthesis methods can play in the development and refinement of nursing theory is discussed.

The Science of Research Synthesis

Synthesis of research is a scientific endeavour that involves the critical appraisal of existing findings for the purpose of cumulation or integration (Cooper & Hedges, 1994; Light & Pillemer, 1984; Noblit & Hare, 1988; Paterson, Thorne, Canam, & Jillings, 2001). It is used to discover the consistencies and account for the variability among studies of the same question (Cooper & Hedges, 1994). The aim of research synthesis is to integrate evidence from multiple studies into a coherent, accessible product.

Systematic review, a synthesis method, makes use of explicit procedures to identify, critically evaluate, and summarize the existing research relevant to a specific question (Alderson, Green, & Higgins, 2004; Chalmers, Hedges, & Cooper, 2002; Egger & Davey Smith, 1997). The format is specifically designed to reduce the bias inherent in unsystematic, informal narrative or integrative reviews, and to parallel traditional methods of scientific inquiry (Cook, Mulrow & Haynes, 1997; Egger et al, 2001). Systematic review has been primarily associated with the synthesis of quantitative research, in particular randomized controlled trials (RCTs).

Research synthesis also involves two methods for combining the data or findings from primary studies. Meta-analysis is the statistical synthesis of data from discrete but comparable primary quantitative studies included in a systematic review. Meta-synthesis refers to a family of methodological approaches focused on the analysis, synthesis and re-interpretation of existing qualitative findings (Thorne et al., 2004).

It is always appropriate to conduct a systematic review of the literature in order to summarize the "state of the science" about a phenomenon of interest. It may be inappropriate to attempt to "put together" or integrate the findings from multiple studies using meta-analysis or meta-synthesis techniques if the primary studies on the topic are not comparable or do not examine the same phenomenon. Accordingly, synthesis of findings using meta-analysis or meta-synthesis techniques may or may not be pursued as part of a systematic review depending on the commensurability of the findings (Light & Pillemer, 1984; Noblit & Hare, 1988).

Multiple primary studies of the same question serve as the *subjects* of synthesis research and provide the material (data and findings) for integration. The context and particulars of each individual study are maintained during analysis. This permits comparison of features of the studies that may influence results and affect the generalizability of the synthesis (Cooper & Hedges, 1994; Jensen & Allen, 1996; Light & Pillemer, 1984; McCormick, Rodney, & Varcoe, 2003).

The methods employed for synthesis of quantitative and qualitative research are significantly different and are distinguished by the nature of the question and by the selection and analyses of quantitative data or qualitative findings. However, their aims are analogous in that both endeavour to systematically "take stock" of what is known, and to produce more credible, comprehensive, and precise answers to research questions than can be achieved in a single study. This paper addresses the synthesis of quantitative research only.

Detailed accounts of the discrete procedures of quantitative research synthesis are beyond the scope of this paper and they are described in detail elsewhere (e.g. Cooper & Hedges, 1994; Egger et al., 2001; Hunter et al, 1982; Light & Pillemer, 1984; Petitti, 2000; Sutton, Abrams, Jones, Sheldon & Song, 1998). In the following section a brief overview of the basic steps of quantitative research synthesis and the key issues arising in synthesis research are presented.

Problem Formulation

For the synthesis of quantitative research, the first step is to articulate the questions of interest and objectives for the systematic review. These are used to define the review's eligibility criteria and to determine what studies will be included. Whether the review will be hypothesis testing or hypothesis generating is established before the review commences. A plan to test specific hypotheses influences and limits the selection of primary studies. Alternately, a broad approach to a body of work means that diverse studies can be included, which will help in the development of hypotheses (Light & Pillemer, 1984).

In seeking answers to what is known about a particular phenomenon, those who carry out research synthesis develop an investigative strategy (research protocol). They ask questions such as:

1. What precise question about the phenomenon will the synthesis address?
2. What is the nature of the synthesis – will it be exploratory in nature (hypotheses-generating) or be built around testable hypotheses or the subjective meaning of a phenomenon?
3. What type of data (i.e. primary studies) should be included?

4. What are the relevant populations, situations, methodological characteristics, and theoretical frameworks of the primary studies that are of interest for the synthesis?
5. What is the potential for the synthesis to create new knowledge, resolve controversies, and expand understanding of the phenomenon?

Controlled trials are generally preferred when asking questions about the effectiveness of interventions because it is assumed that their design reduces bias and ensures validity of the trial results (Egger et al., 2001; Kleijnen, Gotzsche, Kunz, Oxman & Chalmers, 1997). Strict adherence to a predetermined protocol arising from the research question avoids introduction of bias from preferential inclusion or exclusion of data (studies) or post hoc changes to the investigative plan once the study is commenced (Egger et al., 2001; Felson, 1992).

Data Collection

Data collection involves the identification and selection of primary studies for inclusion in the review and the extraction of data from the study reports. Exclusion or omission of studies that are unpublished, have limited distribution, are not indexed in the major bibliographic databases (grey literature) or are not published in the English language will produce a deficient subset of the total applicable evidence. The result will be a publication bias. As well, multiple publications of original data from a single study create the illusion of more data than actually exists. Selective reporting of some but not all outcome data based on results can also contribute to biased, inaccurate effect estimates (Egger & Davey Smith, 1998; Felson, 1992).

Ideally, the intent is to include all relevant studies in the review, and to this end a detailed plan is devised *a priori* to maximize the sensitivity and precision of the literature search (Egger et al., 2001; Klassen, Jadad, & Moher, 1998; Petitti, 2000). Comprehensive search strategies including computerized scrutiny of bibliographic databases, cross checks of references from review articles; contacts with experts in the field; and hand searching of relevant journals are employed to identify relevant studies (Clarke & Oxman, 2001; Egger et al., 2001; Petitti, 2000; White, 1994). As is the case in primary quantitative research, the fundamental question is about the representativeness of the sample of primary studies obtained from the literature, and the degree to which it supports inferences of generalizability to the population or the universe of interest (Hedges, 1994).

Quality Assessment – Data Evaluation

The results of research synthesis are dependent on the internal validity of the primary research studies included in the review. Internal validity, "the basic minimum without which any experiment is un-interpretable" (Campbell & Stanley, 1963), is threatened by bias which can be intrinsic in the primary studies, or become a factor during synthesis.

Synthesis cannot overcome bias in the conduct of primary studies. For that reason, quality assessment is undertaken to evaluate the strategies taken to minimize bias. A variety of assessment scales and checklists are available for this purpose but results can depend on the choice of a tool, and interpretation of scores is problematic. As an alternative, examination of individual components of quality such as concealment of treatment allocation, blinding of intervention and outcome assessment, and procedures for dealing with subject attrition in analysis is recommended (Juni, Altman, & Egger, 2001). Methological research has shown that inadequate allocation concealment and lack of blinding in quantitative studies are associated with exaggeration of treatment effect estimates (Schultz, Chalmers, Hayes, & Altman, 1995), and consequently, these are a primary focus for quality assessment.

Data Analysis and Interpretation

The statistical synthesis of data from discrete but comparable primary quantitative studies included in a systematic review is referred to as meta-analysis. The aim of meta-analysis is to merge and average the data (usually reported as means and standard deviations) from the primary studies in order to aggregate the findings into a single estimate of the effect of an intervention (Cooper & Hedges, 1994; Glass, 1976; Hunter et al., 1982; O'Flynn, 1999). By pooling the results of many small trials, meta-analysis increases power to determine a more accurate summary estimate. Effect size is the statistic of choice for aggregation of quantitative data and can be conceptualized as the magnitude of the relationship between two variables. The clinical significance of the effect size is readily apparent (Glass, 1976).

Selection of the statistical methods for a particular meta-analysis is based on the data type (binary or continuous), choice of the summary statistic, and on observed heterogeneity among studies (the extent to which the results are consistent across studies) (Egger et al., 2001). Assessment of heterogeneity is essential to determine if there are important differences in the results or if the variation can be attributed to chance alone (Higgins, Thompson, Deeks, & Altman, 2003).

The results of meta-analysis are normally considered to be descriptive in nature as opposed to inferential. Procedures such as random allocation, experimental manipulation of a variable, and other controls enhance capacity for cause and effect inference in primary studies. Inclusion of primary studies that possess these characteristics strengthen the conclusions arising from meta-analysis and may justify inferences of cause and effect from the results of the meta-analysis (Hall, Tickle-Degnen, Rosenthal, & Mosteller, 1994), and contribute to the development of explanatory and predictive theory.

Meta-analysis can take more than one approach. The most basic involves the aggregation of primary study findings to test the validity of a hypothesized relationship. Analysis at this level yields a mean effect size and establishes whether the difference between the treatment groups is statistically significant. Examination of the variables that diminish the effect size and exploration of the sources of variability in outcomes across studies can provide information about the generalizability of the results beyond the primary studies. Theoretical hypotheses not considered in the primary research studies can also be tested if sufficient information is included in the trial report (Miller & Pollack, 1994).

For example, a meta-analysis of the data from studies comparing dorsal penile nerve block (DPNB) to no treatment for pain during male neonatal circumcision can incorporate each of these approaches. At the first level, aggregation of heart rate (frequently employed as a proxy measure of pain in non-verbal neonates) outcome data tests the relationship between treatment and pain responses, and will yield an effect size that quantifies the degree of difference in the pain responses between the groups. Second, an examination of variables such as gestational age and previous painful experiences can be conducted to reveal whether they account for variability in outcome results across studies and influence effect size. Finally, new hypotheses not examined in the primary studies such as the impact of wait time after anaesthetic administration on pain responses can be subjected to meta-analysis.

Contributions of Research Synthesis

Syntheses of existing research organize findings to answer questions and resolve apparent conflicts in the data from multiple studies. Estimates of the effectiveness of interventions based on the synthesis of quantitative findings can be used to develop recommendations and guidelines for practice, inform the conduct of future investigations, and influence policy (Light & Pillemer, 1984). In the next section, contributions of research synthesis that are of importance to nursing are discussed.

Theory development and refinement. Theory can be defined as a structured set of unambiguous concepts and the propositions that link those concepts. Theories are expressed as descriptions, explanations, and predictions about phenomena. In combination with theory arising from ethical, personal and aesthetic experience and perspectives, empirically derived theories (i.e. those derived from the results of quantitative, qualitative and other types of empirical research) comprise the bulk of disciplinary knowledge base in nursing (Fawcett, Watson, Newman, Hinton Walker & Fitzpatrick, 2001).

Primary quantitative research tests theory that has been expressed as hypotheses about relationships between variables and propositions about cause and effect. Tested hypotheses provide the evidence for development and the expansion of empirical theory. Ultimately these are incorporated as components of more complex theoretical models.

Synthesis creates the opportunity to examine theory derived from individual studies of the same question in light of the similarities and differences across the studies. Through synthesis, the potential is created to enlarge empirical theory to reflect the body of research as a whole. Theory that is proposed or expanded based on the results of synthesis of multiple studies is considered to be more comprehensive and credible than what can be derived from a single study (Estabrooks, Field, & Morse, 1994; Finfgeld, 2004; Hunter et al., 1982; Thorne et al., 2004). For that reason, synthesis can contribute to the refinement of empirical theory and the advancement of nursing knowledge based on empirically-derived theory (Estabrooks et al., 1994; Paterson et al., 2001).

Evidence-based practice. Nurses and other healthcare professionals face increasing demands for accountability in their practice. However, the notion that accountability is assured through adoption of the principles of evidence-based practice (EBP) has engendered considerable controversy in nursing. EBP has been characterized as the mantra of the moment (Jennings & Loan, 2001), a growth industry (Estabrooks, 1998), and as "a barren possibility… [which] obstructs nursing process, human care and professional accountability" (Mitchell, 1999, p. 30). Advocates maintain that nursing is responsible to identify and provide only the care that is known to be effective and that EBP will focus the discipline on establishing what types of evidence demonstrate effectiveness in nursing practice (DiCenso & Cullum, 1998; Mulhall, 1998).

Those in opposition argue that instead of enhancing the quality of care, EBP undermines individualized decision-making. Fears that the EBP movement will legitimize and mandate "cookbook" approaches to patient care are widespread and have been intensified by organizational moves to develop EBP guidelines that focus on best care as well as cost-containment (Closs & Cheater, 1999; Mitchell, 1997). At the same time, nurses have issues with accessing and appraising available evidence. Many practicing nurses cannot or choose not to access research evidence; they are also not able to evaluate its validity for their practice (Estabrooks, 1998; Mulhall, 1998; Upton, 1999).

In order to be accountable for practice nursing must determine what constitutes relevant evidence and by what methods the evidence to guide practice is most effectively and efficiently accumulated. Synthesis methods have great potential to advance the work of "putting together" empirical evidence and linking it with practice. For example, a systematic review will inform the development of clinical guidelines that have the potential to influence individual and group practice in a defined area. Alternately, the results of a systematic review may be incorporated in the form of policy that establishes a minimum standard for practice, and clarifies expectations about a consistent approach to providing nursing care.

Initiatives are needed to help overcome some of the barriers to locating, appraising and using the available empirical evidence. Access to completed reviews is addressed in part through the Cochrane Collaboration, an international organization that produces and disseminates systematic reviews of healthcare interventions through quarterly publications in the on-line Cochrane Library. Similarly, journals such as *Evidence-based Nursing* select, abstract, and summarize qualitative and quantitative primary and review articles from the healthcare literature that are of particular interest to nursing. Commentary by clinical experts is included to assist practitioners in assessing the clinical relevance of the summaries (Ciliska, Pinelli, DiCenso & Cullum, 2001;

DiCenso, Cullum, Ciliska, & Marks, 2000). The journal is also available online at the website – *www.evidencebasednursing.com*.

Protected time for clinical nursing leaders is vitally important if they are to maintain up to date knowledge of the literature, including systematic reviews. Support for post-graduate and continuing education to develop critical analysis skills in the nursing workforce has been slow to develop but is likely to gain momentum with the increasing emphasis on evidence-based practice.

Research. Carrying out a research synthesis requires skill. Training in the use of synthesis methods and knowledge of the content area in which the synthesis is conducted are essential. Courses ought to be offered in graduate programs to ensure that nurse scientists have the skills and expertise to use synthesis methods.

Research synthesis can facilitate improvements in the design of primary studies. Systematic reviews are becoming a standard prerequisite in planning for the conduct of primary studies, and they should assist researchers to avoid repeating previous mistakes or pursuing useless lines of investigation. Further development of methods for synthesis of qualitative research will improve recognition of the contribution of qualitative research can make to the disciplinary knowledge base.

Conclusions

Research synthesis stands to make a major contribution to knowledge development in the discipline of nursing. Synthesis becomes an effective tool for knowledge development when evidence from many studies is systematically and rigorously integrated to create a more reliable, comprehensive, and credible understanding of phenomena. Empirical theory, which is the articulation of relationships and knowledge obtained through research, is substantiated and refined through synthesis.

To date, research synthesis in health care has been chiefly focused on evaluation of the effectiveness of interventions based on data acquired through randomized controlled trials. Knowledge about the effectiveness of interventions is important, but not sufficient to guide nursing practice. Coupled with the results of quantitative research synthesis, the increasing availability of cumulative qualitative findings will contribute to the enhancement of discipline-specific knowledge, and advance appreciation of research synthesis as an essential tool of nursing science.

It has been said that the science of research synthesis is intrinsically inter-disciplinary because it requires that all available evidence that is relevant to the question, as opposed to discipline-specific evidence, be searched and evaluated (Bausell, 1993). As a result, research synthesis offers an impetus towards interdisciplinary research, and can facilitate significant involvement of nursing with other disciplines to implement effective, evidence-based practice and strategies for care.

As the science of nursing is emerging, research synthesis may prove most useful initially to identify gaps in knowledge relevant to nursing and nursing practice. Review of the nursing research literature using systematic methods will assist nursing to identify what is known about particular phenomena and to make decisions about what investigations are required to expand the theory and knowledge acquired to date. Additionally, synthesis will make evident the historic deficiencies in the design and conduct of investigations in order that these can be improved in future nursing research.

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CHAPTER THREE

Pain Relief for Neonatal Circumcision – Cochrane Review

Errata

An updated version of the Cochrane Review has been submitted to the Cochrane Neonatal Group, in keeping with Cochrane requirements to provide annual updates on published systematic reviews. In the updated version, several errors arising from confusion around the number of subjects randomized in each trial versus the numbers included in analyses of the outcome results in the primary studies were corrected. None of these errors affected the results of the meta-analysis, or the recommendations arising from the systematic review. The corrections will be included in the publication of the next issue of the Cochrane Library (2005, Issue 4), and are as follows **(in bold)**:

- Page 1, 11 - Thirty-five trials involving **1997** newborns were included.
- Page 1, 8 - Six trials involving **200** newborns compared eutectic mixture of analgesics (EMLA) with placebo.
- Page 1, 9 - DPNB, compared with EMLA in **three** trials involving **139** newborns, demonstrated significantly lower heart rate and pain scores.
- Page 1, 9 - When compared with sucrose in two trials involving **127** newborns, DPNB demonstrated less time crying, and lower heart rate.
- Page 8 – Eight trials compared sugar solutions to water and/or no treatment and included **360** subjects.
- Page 8 – Three trials compared topical lidocaine to placebo and included **115** patients.

- Page 14 - Characteristics of Included Studies – Benini – **14** subjects randomized to the petroleum jelly group
- Page 19 - Characteristics of Included Studies – Butler-O'Hara – **25** subjects randomized to each group
- Page 20 - Characteristics of Included Studies – Herschel – **40** subjects randomized to oral sucrose via nipple group
- Page 25 - Characteristics of Included Studies – Lander – total of **54** subjects randomized
- Page 26 - Characteristics of Included Studies – Marchette 1989 – total of **103** subjects randomized
- Page 30 - Characteristics of Included Studies – Stang 1997 – total of **83** subjects randomized
- Page 31 - Characteristics of Included Studies – Taddio – **38** subjects randomized to LP group
- Page 32 - Characteristics of Included Studies – Williamson 1986 – total of **24** subjects randomized
- Page 39 – Additional Tables – 01 – Trials assessing pain/behavior scores – **Delete Taeusch 2002** (excluded study)

Pain relief for neonatal circumcision (Review)

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Pain relief for neonatal circumcision (Review)

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ABSTRACT

Background
Circumcision is a painful procedure that many newborn males undergo in the first few days after birth. Interventions are available to reduce pain at circumcision; however, many newborns are circumcised without pain management.

Objectives
The objective of this review was to assess the effectiveness and safety of interventions for reducing pain at neonatal circumcision.

Search strategy
We searched Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004), MEDLINE (1966 - April 2004), EMBASE (1988 - 2004 week 19), CINAHL (1982 - May week 1 2004), Dissertation Abstracts (1986 - May 2004), Proceedings of the World Congress on Pain (1993 - 1999), and reference lists of articles. Language restrictions were not imposed.

Selection criteria
Randomised controlled trials comparing pain interventions with placebo or no treatment or comparing two active pain interventions in male term or preterm infants undergoing circumcision.

Data collection and analysis
Two independent reviewers assessed trial quality and extracted data. Ten authors were contacted for additional information. Adverse effects information was obtained from the trial reports. For meta-analysis, data on a continuous scale were reported as weighted mean difference (WMD) or, when the units were not compatible, as standardized mean difference.

Main results
Thirty-five trials involving 1,984 newborns were included. Thirty-three trials enrolled healthy, full term neonates, and two enrolled infants born preterm.

Fourteen trials involving 592 newborns compared dorsal penile nerve block (DPNB) with placebo or no treatment. Compared to placebo/no treatment, DPNB demonstrated significantly lower heart rate [WMD -35 bpm, 95% CI -41 to -30], decreased time crying [WMD -54 %, 95% CI -64 to -44], and increased oxygen saturation [WMD 3.2 %, 95% CI 2.7 to 3.7]. Six trials involving 190 newborns compared eutectic mixture of analgesics (EMLA) with placebo. EMLA demonstrated significantly lower facial action scores [WMD -46.5, 95% CI -80.4 to -12.6], decreased time crying [WMD - 15.8 %, 95% CI -20.8 to -6.8] and lower heart rate [WMD -15 bpm, 95% CI -19 to -10]. DPNB, compared with EMLA in four trials involving 164 newborns, demonstrated significantly lower heart rate [WMD -17 bpm, 95% CI -23 to -11] and pain scores. When compared with sucrose in two trials involving 126 newborns, DPNB demonstrated less time crying [MD -166 s, 95% CI -211 to -121], and lower heart rate [WMD -27 bpm, 95% CI -33 to -20]. Results obtained for trials comparing oral sucrose and oral analgesics to placebo, and trials of environmental modification were either inconsistent or were not significantly different.

Adverse effects included gagging, choking, and emesis in placebo/untreated groups. Minor bleeding, swelling and hematoma were reported with DPNB. Erythema and mild skin pallor were observed with the use of EMLA. Methaemoglobin levels were evaluated in two trials of EMLA, and results were within normal limits.

Authors' conclusions

DPNB was the most frequently studied intervention and was the most effective for circumcision pain. Compared to placebo, EMLA was also effective, but was not as effective as DPNB. Both interventions appear to be safe for use in newborns. None of the studied interventions completely eliminated the pain response to circumcision.

SYNOPSIS

Synopsis pending.

BACKGROUND

Neither the American Academy of Pediatrics nor the Canadian Paediatric Society recommends routine or elective circumcision of the male newborn. Nevertheless, elective circumcision of male newborns is commonly performed in the first few days after birth. Approximately 1.2 million newborn males are circumcised in the United States annually at a cost of 150 to 270 million dollars (AAP 1999). Precise Canadian data are not available because the procedure has been delisted in many provinces, but it is estimated that 48% of male neonates born in Canada are circumcised (CPS 1996). The practice of male neonatal circumcision is not limited to North America; it is performed worldwide for religious and cultural reasons.

As an invasive, painful procedure, unanaesthetized circumcision elicits systemic stress responses in the vulnerable newborn which negatively affect major body systems. Documented physiological and behavioral responses include increased output of adrenal corticoids (Gunnar 1981; Talbert 1976), increased heart rate and respiratory rate, decreased arterial oxygen (Rawlings 1980), skin flushing, vomiting and cyanosis (Poma 1980), changes in sleep/wake state, increased crying (Anders 1974; Gunnar 1981), and diminished responsiveness to parents (Dixon 1984). Unanaesthetized circumcision has also been linked with complications such as apnea and choking (Lander 1997), gastric rupture (Connelly 1992), and recurrence of pneumothorax (Auerbach 1978). Infants circumcised without anaesthesia exhibit stronger pain responses to routine immunizations during the first six months of life than infants who were not circumcised (Taddio 1997b), suggesting that circumcision pain may exert long term effects on infant behavior.

INTERVENTIONS FOR CIRCUMCISION PAIN

Numerous interventions to prevent or reduce circumcision pain have been examined. These include penile blocks, topical anaesthetics, oral analgesia and sucrose administration, non-nutritive sucking, music and other environmental interventions.

The technique of dorsal penile nerve block (DPNB) for newborn circumcision was first described in 1978 (Kirya 1978), and it has since been extensively evaluated. More recently, subpubic (Dalens 1989) and penile ring block techniques (Hardwick Smith 1998; Lander 1997) have been examined. Adverse effects of penile blocks appear to be limited to bruising and slight bleeding at the injection site (Snellman 1995). Of note, the rapidity of onset of the anaesthetic used for penile blocks (generally 1% lidocaine without epinephrine) is intermediate and a "wait time" of 5 minutes is recommended to achieve anaesthesia (Taddio 2001). Wait time is a concern for clinicians because it increases the total time required for the circumcision surgery; however, inadequate "wait time" influences anaesthetic effect (Kharasch 2003).

Several types of topical anaesthetics have been used for neonatal circumcision, including eutectic mixture of local anaesthetics (EMLA) and 4 to 30% lidocaine creams. EMLA is a water-based cream that contains 2.5% lidocaine and 2.5% prilocaine. Compared with placebo, EMLA attenuates the pain responses of increased heart rate, facial activity and crying, and decreased oxygen saturation (Lander 1997; Taddio 1997). A meta-analysis of three studies examining this intervention indicated that the use of EMLA results in a significantly lower increase in heart rate (from baseline) and less crying during the various phases of circumcision surgery compared to placebo. In two of the included studies, lower facial action scores suggested less pain in the EMLA treated groups compared to placebo (Taddio 2002).

Potential difficulties with drug administration and the presurgical wait time may limit the feasibility of topical anaesthesia as a pain intervention for circumcision in many settings (Lander 1997). Considerable technical skill is required to apply the drug, and to secure the occlusive dressing needed to keep it in place. For adequate absorption, EMLA must be applied for at least 60 minutes prior to surgery (Taddio 1998), and must be reapplied if the infant voids during the wait time.

Methaemoglobinaemia (MetHb), caused by oxidation of haemoglobin by the metabolites of prilocaine, is a serious but relatively rare risk associated with EMLA use in infants less than 12 months of age. A recent systematic review of the use of EMLA for acute pain in infants demonstrated that the risk of significant MetHb is low with single dose applications of 0.5 to 2g applied for 10 - 180 minutes for full term neonates, and 0.5 to 1.25g applied for 3 to 180 minutes for preterm neonates (Taddio 1998). Local skin reactions, such as blanching, erythema, and edema of the skin have been reported with the use of EMLA , but these are usually transient and not considered serious.

Sucrose or other sugar solutions alone or in combination with non-nutritive sucking have recently been recommended as interventions for procedural pain management (Mitchell 2000). Oral sucrose is thought to activate central endogenous pathways, and may stimulate release of endorphins from the hypothalamus. Non nutritive sucking (NNS) is also thought to have an analgesic-like effect through stimulation of orotactile and mechanoreceptor mechanisms (Gibbons 2001; Mitchell 2003). The sensations created by NNS may deflect attention away from pain and facilitate self regulation because the infant is in control of the sucking. Sucrose and NNS appear to operate synergistically when offered in combination, and may provide more effective pain relief (Carbajal 1999; Gibbons 2001; Gibbons 2002). The analgesic effect of sucrose is activated within two minutes, and lasts for three to five minutes (Haouari 1999; Mitchell 2003). Although sucrose in a wide variety of dosages (concentrations from 12 to 24%, and volumes from 0.05 to 2.0 ml) has generally been found to decrease acute, procedural pain responses in neonates (Mitchell 2000; Stevens 1997), the optimal dose has not yet been identified. Meta-analyses results indicate that a 0.24g dose is effective to reduce pain responses in term infants, and higher doses do not appear to increase effectiveness (Stevens 1997). In comparison, relatively small doses (0.01 to 0.02g) appear to be effective for preterm infants (Johnston 1997). Interest in sucrose or other sugar solutions as a single or adjunctive intervention for circumcision pain is reflected in the design of recent research (e.g. Kass 2001; Kaufman 2002).

Acetaminophen is the most frequently prescribed non-opioid oral analgesic used to treat mild to moderate pain in pediatric populations (Berde 2002; McGrath 1990). Acetaminophen is safe and effective for neonates and can be administered orally or rectally (Stevens 1999). Acetaminophen has been used as an intervention for circumcision pain (Howard 1994).

A variety of non-pharmacological interventions have been evaluated for treatment of acute procedural pain in neonates. In theory, these interventions provide nonpainful stimuli that compete with painful stimuli for the neonate's attention, and thus may blunt the perception of pain (Bellieni 2002). Interventions such as rocking, massage, facilitated tucking, and cuddling reduce pain responses during invasive procedures (Campos 1994; Corff 1995; Gray 2000). Music and other sounds (intrauterine, heartbeat) provide an auditory stimulus which may modulate pain perception and these have been evaluated as interventions for circumcision pain (Marchette 1989; Marchette 1991).

NEONATAL PAIN RESPONSES

It is difficult to evaluate the effectiveness of interventions for circumcision pain because newborns are non-verbal and display stereotypic responses to a variety of painful and non-painful stimuli. To maximize the validity of pain assessment in newborn populations three classes of pain indicators or outcomes, biochemical, physiological, and behavioural, are generally employed for research. Salivary and serum cortisol, the most frequently measured biochemical indicators, serve as markers of the stress response to pain because hormones of the hypothalamic-pituitary-adrenal axis are assayed. Physiological indicators include heart rate, respiratory rate, blood pressure, transcutaneous oxygen saturation (Tc pO2), transcutaneous carbon dioxide (Tc pCO2), oxygen saturation (SaO2), palmar sweat, intracranial pressure (ICP) and vagal tone. In newborn populations, heart rate is the most frequently studied physiological indicator (Sweet 1998). Behavioral indicators include facial expression, cry, gross motor movement, and changes in behavioral state. Facial expression (Grunau 1987) is the most comprehensively studied behavioral indicator for neonatal pain.

Multidimensional measurement tools that employ more than one parameter usually contain physiological and behavioral indicators, and occasionally add contextual information to obtain an overall pain score. The Neonatal Infant Pain Scale (NIPS) (Lawrence 1993) and the Premature Infant Pain Profile (PIPP) (Stevens 1996) are multidimensional tools frequently utilized as outcome measures for investigation of acute procedural pain in term and preterm neonates. Although a number of pain measures are available for use with neonatal populations, no single measure has proven to be the best for all situations. Accordingly, all outcomes evaluated in the included studies as measures of neonatal pain were included in this review.

SUMMARY

The substantial amount of research conducted to date suggests a willingness to address the problem of circumcision pain. However, the majority of neonates are circumcised without interventions for pain (Myron 1991; Ryan 1994; Snellman 1995; Wellington 1993). This situation persists despite growing awareness that newborns may perceive pain more intensely than older children or adults (Anand 2001; Fitzgerald 1993) and can be significantly compromised by it.

It has been suggested that training to manage circumcision pain is inadequate to promote consistent use of available interventions (Howard 1998). Recent surveys indicate that significant numbers of obstetricians (75%), family practitioners (44%), and pediatricians (29%) do not use analgesia/anaesthesia for circumcision because of concerns about adverse drug effects or because they believe that the procedure does not require pain management (Maxwell 1999; Stang 1991; Stang 1998).

Although a wide variety of interventions for circumcision pain have been examined, the individual and relative effectiveness of each has not been systematically assessed. Thus, the apparent reluctance of practitioners to adopt the regular use of pain interventions for circumcision may reflect beliefs that the findings of research conducted to date are collectively un-interpretable. At the same time, negative perceptions of the technical and practical difficulties associated with pain interventions may diminish clinician motivation to implement their regular use.

A systematic review of the research in this area was needed to summarize and identify implications arising from the existing evidence, and to provide an informed basis for practice and to identify gaps in knowledge which require further investigation. This review adds to knowledge gained from a previous systematic review which examined the efficacy of a single intervention for circumcision pain (Taddio 2002) by evaluating the efficacy and safety of all interventions for reducing pain at neonatal circumcision.

OBJECTIVES

To determine the safety and effectiveness of interventions to relieve pain associated with neonatal circumcision. Subgroup analyses were prespecified according to wait time (after anaesthetic administration and prior to start of surgery) for penile blocks, and for dose delivered for sucrose interventions.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs). Studies reported only as abstracts were included if relevant.

Types of participants

Male term or preterm neonates undergoing circumcision during the neonatal period (with postnatal age maximum of 28 days after reaching 40 weeks corrected gestational age).

Types of intervention

Any intervention intended to relieve pain during the circumcision procedure, for example, penile blocks, topical anaesthetics, oral sucrose administration, oral analgesics, surgical devices or techniques, or environmental manipulation such as music therapy or special restraints. This review included trials of interventions for circumcision pain in which any intervention was compared with placebo, no treatment, or with another active intervention.

Types of outcome measures

The primary outcome was pain as assessed by:

1. Physiological variables, such as heart rate (HR), respiratory rate (RR), oxygen saturation, or blood pressure (whether reported as change in, mean or absolute values)
2. Biochemical variables, such as salivary or serum cortisol levels (whether reported as pre- and post- measures or as change from baseline values)
3. Cry variables, for example, latency and duration of first cry, total cry duration, and/or percentage of time crying during the circumcision procedure
4. Validated pain measures, for example:
- Neonatal Infant Pain Score (Lawrence 1993);
- Neonatal Facial Action Coding System (Grunau 1987);
- Premature Infant Pain Profile (Stevens 1996);
- Other pain measures.

Secondary outcomes:

Complications of pain interventions were assessed as secondary outcomes. The outcomes included but were not limited to:
1) occurrence/incidence of methaemoglobinaemia (topical anaesthesia)
2) blanching and local skin irritations (topical anaesthesia)
3) bleeding, bruising and hematoma formation (penile blocks)
4) behavioral responses such a choking, spitting up, etc. during circumcision (all interventions)

Difficulties encountered in implementation of pain interventions, as reported by researchers, were noted.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Neonatal Group search strategy

Standard methods as per the guidelines of the Cochrane Neonatal Review Group (CNRG) were utilized.
1. CIRCUMCISION/exp
2. circumcision surgery.mp
3. newborn circumcision.mp
4. 1 OR 2 OR 3
5. local anaesthes*
6. penile block.mp/exp
7. dorsal penile nerve block.mp/exp
8. ring block.mp/exp
9. 5 OR 6 OR 7 OR 8
10. eutectic mixture of local anaesthetics.mp/exp
11. EMLA.mp/exp
12. LIDOCAINE.mp/exp
13. 10 OR 11 OR 12
14. acetaminophen.mp/ OR paracetamol.mp/exp
15. sucrose.mp
16. pacifiers.mp
17. music therapy.mp
18. Gomco clamp.mp
19. Mogen clamp.mp
20. 9 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 4 AND 20

22. HUMAN
23. MALE
24. 22 and 23
25. infant, newborn
26. neonat*
27. 25 OR 26
28. 24 AND 27
29. 21 AND 28
30. clinical trial
31. 29 AND 30

Databases searched included: Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004; MEDLINE 1966 - April 2004; EMBASE 1988 - 2004 week 19; CINAHL 1982 - May week 1 2004; PubMed 1966 - May 2004; Web of Science 1975 - May 2004; Dissertation Abstracts 1986 - May 2004. Keywords and (MeSH) terms included infant/newborn, male, circumcision, penile blocks, sucrose, lidocaine, EMLA, acetaminophen. Abstracts of the World Congress on Pain were searched for the years 1993 - 1999 inclusive. Reference lists of all articles were screened to identify any additional studies. Language restrictions were not imposed.

METHODS OF THE REVIEW

Study Selection

The titles and abstracts of all reports identified through the electronic and other searches were scanned independently by two reviewers and full study reports were obtained for those that appeared to meet the inclusion criteria. Study reports were then evaluated independently by two reviewers for possible inclusion in the review. Disagreements were resolved by consensus. Studies rejected at this stage were included in the Table of Excluded Studies.

Quality Assessment

Assessment of the quality of all included studies was undertaken independently by two reviewers as a component of the data extraction process. Standard methods of the CNRG were used to assess: 1) the randomisation procedure, 2) concealment of allocation/blinding of randomisation, 3) blinding of intervention, 4) subject attrition and follow-up, and 5) blinding of outcome measurement. As per the CNRG guidelines, an overall quality score was not assigned. Reviewers were not blind to trial authors or institutions during the study selection or quality assessment processes.

Data Extraction

Data were extracted from included studies by two independent reviewers using a data extraction form designed specifically for this review. The data extraction form was developed in a draft format and piloted on several studies and modified as required before use. The reviewers abstracted data independently, compared results and resolved differences.

Sixteen trials included in this review either did not report outcome data, or did not report data in a format that could be analysed in this review (Arnett 1990; Benini 1993; Blass 1991 A; Holliday 1999; Holve 1983, Joyce 2001; Kass 2001; Marchette 1989; Marchette 1991; Maxwell 1987; Mohan 1998; Mudge 1989; Spencer 1992; Williamson 1997; Zahorodny 1998; Zahorodny 1999). Additional information was sought from ten authors and means and standard deviations were subsequently obtained for three trials (Benini 1993; Joyce 2001; Kass 2001). Where means and standard deviations were not available, data were imputed or derived from graphs contained in the reports (Arnett 1990; Benini 1993; Blass 1991 A; Holliday 1999; Maxwell 1987; Mohan 1998; Mudge 1989; Taddio 1997). Missing standard deviations were either calculated from other summary statistics or imputed using singular or mean standard deviations from similar trials.

Several authors reported total sample size only and information about the number of subjects per group was obtained from the authors (Benini 1993; Joyce 2001). When additional information about sample size could not be obtained from the authors, we assumed equal distribution to study groups in our data analyses (Blass 1991 A; Zahorodny 1998; Zahorodny 1999).

Data Analysis

The outcomes presented in this review were reported as results obtained during the whole circumcision procedure. Usually, the circumcision surgery was described as commencing with application of forceps to the dorsal foreskin of the penis (referred to as dorsal or lateral clamping) and ending with removal of the surgical clamp (the Gomco, Mogen, or Plastibell surgical device, also referred to as a clamp). Some authors reported a single numerical outcome result for the entire circumcision procedure (e.g. Butler O'Hara 1998; Howard 1999; Maxwell 1987; Taddio 1997). Others reported numerical results by procedure phase or step (e.g. dorsal foreskin grasped with forceps, adhesion lysis, dorsal incision, surgical clamp application, foreskin amputation, surgical clamp removal) (Benini 1993; Lander 1997; Woodman 1999). For the latter studies, depending on the outcome, we calculated either the arithmetic mean (e.g. heart rate) or total (e.g. time crying) across the phases or steps of the circumcision (as defined by the authors), and did not include the baseline or recovery phase data. Variance formulae for these arithmetic means and these totals were derived according to the general formula for linear combinations of variance (i.e. $\mathrm{Var}(X+Y) = \mathrm{Var}(x) + \mathrm{Var}(Y) + 2\mathrm{Cov}(X,Y)$). We assumed a correlation of 0.5 as proposed by Follmann 1992. Additional Tables 1 - 7 provide specific details on summary estimate extractions from the included studies.

Data were analysed using the statistical package (RevMan 4.2) provided by the Cochrane Collaboration. When two or more studies were identified that examined the same comparison and clinically similar outcomes, data were pooled using fixed effects. Random effects accounting for inter-study heterogeneity were considered in sensitivity analyses. Studies that compared an active intervention with placebo were analysed separately from those that compared the same active intervention with no treatment.

Continuous data summaries are reported as weighted mean differences (WMD) when the units provided were compatible. When the units were not compatible, the standardized mean difference (SMD) is reported. The SMD describes the difference between the treatments in terms of units of standard deviations (SDs). To improve interpretability, we also report estimates of WMDs derived from the estimated SMDs. To derive the WMDs from the SMDs, we selected either the unit used in the majority of the trials or the most clinically relevant unit under a particular comparison and pooled the available SDs from the trials that used that unit. We then multiplied this pooled SD by the SMD to obtain an estimate of the WMD. The WMDs thus derived are reported along side the SMDs in the results. An example of how a SMD was converted to a WMD is provided in Figure 1.

Individual study outcomes were reported as both final values (FVs) and change from baseline values (CVs). It is appropriate to combine FVs and CVs when combining mean differences to calculate a WMD. However, it is not appropriate, generally, to combine FVs and CVs when combining SMD to calculate an overall SMD. CVs often have smaller standard errors (SEs) than FVs since some of the intra-patient variation is removed from their SEs. Thus the individual study CV SMD tend to be in smaller SD units than the individual study FV SMD. However, in this systematic review, many of the SEs for CVs were either within the range of the FV SEs or they were larger, which is counterintuitive to the argument presented here. Hence, some of the SMD calculated in this review do combine CVs and FVs (Metagraphs 01.03; 01.08; 01.09; 03.02). Additional Tables 1 - 7 provide specific details on summary estimate extractions from the included studies.

Heterogeneity was assessed quantitatively with the I-squared statistic (Higgins 2003). The I-squared statistic indicates the percent variability due to between study (or inter-study) variability as opposed to within study (or intra-study) variability. An I-squared greater than 50% may be considered large. Only non-null heterogeneity statistics are presented here. Too few studies under a single comparison did not allow for any assessment of publication bias nor extensive sub-group or sensitivity analyses. However, post-hoc, we selected heart rate (the most frequently reported outcome) for between-study subgroup analyses using a chi-square method proposed by Deeks 2001. We selected the following subgroup analyses a priori: for penile block interventions, "wait time" from anaesthesia administration to start of the circumcision procedure were considered by the following three categories: no wait time reported, wait time </= 5 minutes, wait time >/= 5 minutes; for sucrose administration interventions, dose of sucrose administered was to be considered but could not be due to the lack of information provided in the reports. Surgical clamp type, use of pacifiers as a co-intervention, and choice of control group were selected for consideration post-hoc.

DESCRIPTION OF STUDIES

210 unique references were identified through search of the electronic databases. The full text of forty-two potentially relevant articles were obtained and reviewed for possible inclusion in this review. Six studies were excluded (see Table - Characteristics of Excluded Studies). In two excluded studies, subjects were not randomised and the intervention was chosen by the attending physician (Malnory 2003; Olson 1998). Two of the excluded studies had no comparison group (Mintz 1989, Russell 1996). One study was a cohort design and the outcome data for the control group was obtained from a previously conducted trial (Taddio 2000), and one (Taeusch 2002) was a head to head comparison of surgical clamps used for the circumcision procedure rather than a direct comparison of interventions for pain relief.

Thirty-five studies (thirty-six reports) were included in this systematic review. Details of each are given in the Table - Characteristics of Included Studies. Two reports outlined different outcome data from the same trial (Dixon 1984, Holve 1983). Two trials were reported as abstracts only (Zahorodny 1998, Zahorodny 1999) and we were unable to obtain additional information from the authors. One unpublished report of Master's thesis research was included (Zolnoski 1993).

Thirty-three of the thirty-five included studies enrolled healthy, full term neonates. One trial included infants born preterm (and less than 28 days age after reaching 40 weeks corrected gestational age) who were ready for discharge from the neonatal intensive care unit (NICU) at the time of circumcision (Butler O'Hara 1998), and one trial enrolled infants born preterm and weighing 1600 - 2500g at the time of circumcision (Holliday 1999).

Nineteen trials examined the effectiveness of penile blocks (Arnett 1990; Butler O'Hara 1998; Hardwick Smith 1998; Herschel 1998; Holliday 1999; Holve 1983; Howard 1999; Kass 2001; Kurtis 1999 A; Lander 1997; Masciello 1990; Maxwell 1987; Newton 1999; Spencer 1992; Stang 1988 A; Stang 1997; Williamson 1983; Williamson 1986; Williamson 1997). Twelve trials assessed topical anaesthetics (EMLA, lidocaine creams) (Benini 1993; Butler O'Hara 1998; Holliday 1999; Howard 1999; Joyce 2001; Lander 1997; Mohan 1998; Mudge 1989; Taddio 1997; Weatherstone 1993; Woodman 1999; Zahorodny 1998), and nine evaluated oral sucrose in a variety of concentrations and doses (Blass 1991 A; Herschel 1998; Kass 2001; Kaufman 2002; Mohan 1998; Stang 1997; Zahorodny 1998; Zahorodny 1999; Zolnoski 1993). In two trials, subjects received an oral analgesic (acetaminophen) (Howard 1994; Macke 2001). Three trials evaluated forms of environmental manipulation (e.g. music, intrauterine sounds) (Joyce 2001;

Marchette 1989; Marchette 1991). For trial details see Table - Characteristics of Included Studies.

In the trials, the interventions were compared with placebo/sham treatments (e.g. saline penile block or inactive topical cream), no treatment, or with other active interventions. In several trials, all subjects received an active baseline intervention (e.g. EMLA cream or DPNB) prior to administration of the study intervention (Butler O'Hara 1998; Kaufman 2002; Stang 1997).

METHODOLOGICAL QUALITY

All of the studies included in this systematic review were described as RCTs. However, fifteen of the study reports provided insufficient information or described inadequate procedures for assurance of blinding of randomisation (see Table - Characteristics of Included Studies). Nine were double-blind for delivery of all interventions (Howard 1994; Howard 1999; Joyce 2001; Macke 2001; Mudge 1989; Taddio 1997; Weatherstone 1993; Woodman 1999; Zolnoski 1993). Some studies compared interventions which could not be masked, for example, block techniques (Masciello 1990; Newton 1999; Spencer 1992). Partial blinding was achieved in several trials through inclusion of a sham or placebo group (Arnett 1990; Blass 1991 A; Holve 1983; Kass 2001; Kaufman 2002; Lander 1997; Stang 1988 A; Stang 1997). Blinding was occasionally achieved on a temporary basis during baseline assessments (Butler O'Hara 1998; Holliday 1999).

There was considerable methodologic diversity between the included studies. For example, there was variation between all of the trials as to what constituted the circumcision "procedure". In one trial (Williamson 1983), outcome data were reported for an undefined three minute "dissection period". In other trials, data were reported for each of multiple steps of a standardized procedure (Benini 1993; Hardwick Smith 1998; Herschel 1998; Lander 1997; Woodman 1999), or reported as a single summary statistic for the entire procedure (Taddio 1997). Other authors did not describe any details of the circumcision procedure followed for the trial (Blass 1991 A; Holliday 1999; Maxwell 1987; Stang 1988 A; Weatherstone 1993). In general, not enough information was provided by authors to be certain that outcome results were directly comparable across studies, as the events that constituted the procedure may not have been equivalent.

There were differences within the group of trials of DPNB (the most frequently studied intervention) in length of time fasting prior to surgery, anaesthetic dose, wait time after anaesthetic administration, and in type of surgical clamp used. In some cases, a single operator performed all circumcisions (Butler O'Hara 1998; Hardwick Smith 1998; Howard 1994), in others, the circumcisions were performed by a number of different operators (Howard 1999; Macke 2001; Stang 1997). Differences in operator technique or in the circumcision procedure could have effected outcome results. For most of the trials, subjects were required to fast prior to the surgery, however, the fasting period varied between trials from 30 - 90 minutes (Arnett 1990; Blass 1991 A; Herschel 1998; Kurtis 1999 A; Maxwell 1987) to 2 - 4 hours (Butler O'Hara 1998; Howard 1994; Kaufman 2002; Masciello 1990). Hunger could have influenced outcomes such as duration of infant crying or other behavioral responses. In a number of studies, subjects were offered pacifiers (Holliday 1999; Howard 1994; Howard 1999; Kurtis 1999 A; Mohan 1998; Spencer 1992; Stang 1997) although pacifiers were not the study intervention. In one trial, all subjects were offered sugar pacifiers (Butler O'Hara 1998). The potential effect of NNS on the outcomes measured in the trials providing pacifiers was not addressed in the reports.

RESULTS

ACTIVE VERSUS PLACEBO OR NO TREATMENT COMPARISONS

- Penile block interventions

Dorsal penile nerve block

Fourteen trials compared dorsal penile nerve block (DPNB) to no treatment or placebo (sham injection). A total of 592 infants were included. Three trials employed pain scores (Metagraph 01.01) as an outcome measure (Arnett 1990; Holliday 1999; Kass 2001). These trials were not combined for meta-analysis of effect on pain because the scores used are not similar in conceptual development or measurement technique. However, outcomes significantly favoured DPNB using all four scores reported: infant irritability score [MD -1.8, 95% CI -2.4 to -1.2], modified behavioral pain scale (MBPS) [MD -3.2 , 95% CI -4.5 to -1.9], Holliday's behaviour score [MD -8.8, 95% CI -11.1 to -6.5], and the crying component of the same behavioral score [MD -9.8, 95% CI -13 to -6.6]. Another behavioral measure, time crying, also significantly favoured the DPNB group [WMD -54 %, 95% CI -64 to -44; SMD -1.74, 95% CI -2.1 to -1.4; Metagraph 01.02; SMD displayed, WMD derived from SMD; data not shown].

Among the physiological measures, heart rate significantly favoured DPNB [WMD - 35 bpm, 95% CI -41 to -30; SMD -1.6, 95% CI -1.8 to -1.3; I2 = 73%; Metagraph 01.03; ; SMD displayed, WMD derived from SMD; data not shown]. Oxygen saturation results also significantly favoured DPNB [WMD 3.2 %, 95% CI 2.7 to 3.7; I2 = 97%; Metagraph 01.06]. Results were heterogeneous, and one author reported the loss of large amounts of data (Herschel 1998). A single trial (Williamson 1983) reported results for transcutaneous oxygen saturation that also significantly favoured DPNB [MD 9.3 torr, 95% CI 1.8 to 16.9; Metagraph 01.07].

Respiratory rate (Metagraph 01.08) and serum B-endorphin (Metagraph 01.12) were not significantly different. Systolic blood pressure was reported in two studies. The combined result was significant and favoured DPNB [WMD -9 mmHg, 95% CI -16 to -

2; SMD -0.66, 95% CI -1.18 to -0.13; I2=92%; Metagraph 01.09; SMD displayed, WMD derived from SMD; data not shown] but the effect was not significant in the random effects model or when Maxwell 1987 was removed. The populations for these two trials were different. Maxwell 1987 recruited healthy newborns in the first few days of life, while Holliday 1999 enrolled low birthweight preterm infants. The preterm infants were cared for NICU and experience with other invasive procedures prior to circumcision may have affected their pain responses.

Serum cortisol (Metagraph 01.10) outcomes were reported in mg/dL, ug/dL and nmol/dL. Results were converted to nmol/dL using standard conversion factors and the outcomes expressed in these units were combined but were not significantly different. A single study (Kurtis 1999 A) reported salivary cortisol results and these were not significantly different.

In two studies (comparing DPNB to no treatment), authors did not report means and SDs. Williamson 1997 found significantly lower oxygen saturation and higher heart rates in the no treatment group during adhesion lysis and application of the surgical clamp (p< 0.001). There was a significant difference in duration of crying between the groups (p <0.001) with the DPNB group crying less. The second study found that the mean increase in heart rate and percent of time crying during circumcision was 50% less for infants in the DPNB group (p< 0.01) (Holve 1983). The DPNB group infants were more attentive to stimuli following circumcision, and were better able to quiet themselves when disturbed (Dixon 1984).

Ring block

Two trials compared ring block to no treatment and included 65 subjects (Hardwick Smith 1998; Lander 1997). Percent time crying was significantly reduced in the ring block group [WMD -26.8%, 95% CI -38.4 to -15.2; SMD -1.27, 95% CI -1.82 to -0.72; I2 = 68%; Metagraph 02.01; SMD displayed, WMD derived from SMD; data not shown]. Only single studies reported other measures. In one (Lander 1997) heart rate significantly favoured the ring block group [MD -29 bpm, 95% CI -52 to -7; Metagraph 02.02]. Oxygen saturation (Metagraph 02.03) and respiratory rate (Metagraph 02.04) were reported by Hardwick Smith 1998 and were not significantly different.

- Topical anaesthetics

EMLA

Six studies compared EMLA to placebo for a total 190 patients (Benini 1993; Joyce 2001; Lander 1997; Taddio 1997; Woodman 1999; Zahorodny 1998). Two studies measured infant behavioral responses using the same pain score, the Neonatal Facial Coding System (Grunau 1987). The trials used the same measure, but the researchers scored a different set of facial actions (see Additional Table 01), and calculated the summary pain score differently. In both summation techniques, a lower score indicated less facial action and less pain. When combined, the results significantly favoured EMLA [WMD -46.5, 95% CI -80.4 to -12.6; SMD -0.6, 95% CI -1.0 to -0.2; Metagraph 03.01; SMD displayed, WMD derived from SMD; data not shown].

Cry time was also significantly decreased with EMLA treatment [WMD - 15.8 %, 95% CI -21 to - 7; SMD -0.78, 95% CI -1.08 to - 0.49; Metagraph 03.02; SMD displayed, WMD derived from SMD; data not shown]. One study (Joyce 2001) did not favour the EMLA treatment, but for this study cry time was measured from the start of circumcision until crying stopped or until 30 minutes elapsed. The other studies measured cry time by phases of the procedure or gave a summary value for the procedure and thus only time spent crying during circumcision surgery could be calculated.

Heart rate was significantly decreased for infants treated with EMLA [WMD -15 bpm, 95% CI -19 to -10; Metagraph 03.03]. The effect on oxygen saturation was not significant [WMD 0.9%, 95% CI -0.2 to 2.0; Metagraph 03.04], and heterogeneity was large (I2= 86%). Respiratory rate, systolic and diastolic blood pressure (Metagraphs 03.05, 03.06, 03.07) were not significantly different.

Lidocaine cream

Three trials compared topical lidocaine to placebo and included 110 patients (Mudge 1989; Weatherstone 1993; Woodman 1999). One study measured percentage of time spent in Brazelton behavioral state 6 (full cry) as a proxy for pain (Weatherstone 1993) and the results were insignificant [MD -8, 95% CI -23 to 7; Metagraph 04.01]. Cry time was significantly reduced [WMD -60 s, 95% CI -99 to -20; Metagraph 04.02] and favoured lidocaine. Heart rate was also significantly reduced [WMD -9 bpm, 95% CI -14 to - 4; I2=12%; Metagraph 04.03]. A single study examined *B*-endorphin levels, and these were significantly reduced for the group treated with lidocaine [MD -49 pg/mL, 95% CI -89 to -9; Metagraph 04.06]. One study (Mudge 1989) did not report standard deviations for oxygen saturation (Metagraph 04.04) and respiratory rate (Metagraph 04.05) and these could not be calculated from the information available. However, the direction of results favoured treatment with lidocaine. Oxygen saturation results for another study (Woodman 1999) were not significantly different.

- Oral sucrose/dextrose

Eight trials compared sugar solutions to water and/or no treatment and included 359 subjects (Blass 1991 A; Herschel 1998; Kass 2001; Kaufman 2002; Stang 1997; Zahorodny 1998; Zahorodny 1999; Zolnoski 1993). A variety of concentrations (24 to 50%) and volumes (1.5 to 10 ml) of sucrose or dextrose were tested. Two studies measured pain scores (Kass 2001; Stang [illegible]997). The results were not combined because the measures are not similar in conceptual development or measurement technique. For example, distress scores (Stang 1997) ranging from 0 to 3 indicated no crying to sustained cry respectively. The modified behavioral pain scale

(MBPS) scores (Kass 2001) ranged from 0 to 10 and incorporated ratings for facial expression, crying and body movements. Results using the behavioral distress score significantly favoured sucrose [MD -0.7 units, 95% CI -1.1 to -0.3], while the MBPS results were not significantly different (Metagraph 05.01).

Cry time results were not significantly different overall [WMD -1.3 %, 95% CI -5.8 to -8.3; SMD 0.07, 95% CI -0.31 to 0.44; I2 = 78%; Metagraph 05.02; SMD displayed, WMD derived from SMD; data not shown]. Individual results from five trials were inconsistent in direction. Zahorodny 1998 reported means only and SDs were substituted from another study using the same intervention and same outcome measure. One study (Kaufman 2002) reported a different measure of cry time. They averaged time spent crying in 10 second intervals, then took the cumulative average of that for each group. In this study, cry time was statistically significant and favoured the sucrose group (56 vs 86 s; P=0.0001). Zahorodny 1999 did not report means or standard deviations, but did report that both the sucrose and the water group cried much less than the no treatment group (p<0.001), and that subjects receiving the sucrose pacifier cried the least (p<.03). The sucrose and water groups in this trial also had smaller increases in heart rate compared to those receiving no intervention (p<.017). These authors did not comment on any differences between the sucrose group and the water group.

The effect on heart rate was not significant [WMD -4 bpm, 95% CI -9 to 2; Metagraph 05.03] overall in three trials. Heterogeneity was large (I2=55%) with two trials favouring the water treatment and one trial favouring the sucrose treatment. In two trials (Herschel 1998; Kass 2001) oxygen saturation was significantly greater in the sucrose group [WMD 1.8%, 95% CI 0.5 to 3.1; Metagraph 05.04] although heterogeneity was again large (I2=88%) and the random effects estimate was not significant [WMD 1.3%, 95% CI -2.7 to 5.2]. Serum cortisol (Metagraph 05.05) was measured in a single study (Stang 1997) and results were not significant.

The inconsistent results in these trials may be related to the volume and concentration of sucrose provided and to the sucrose delivery method. For example, in two studies the treatment group received a dose of 10 ml of 50% sucrose as the treatment intervention (Herschel 1998; Zahorodny 1999), while in two other studies, the treatment group received 2 ml of 50% sucrose (Kass 2001; Zahorodny 1998). The treatment groups in the other trials received 1.5 ml (Blass 1991 A), 2.3 ml (Zolnoski 1993) or an unspecified volume of 24% sucrose (Kaufman 2002; Stang 1997) respectively. The delivery method for the sugar solution also varied between studies. Five administered the sugar/water solution via a nipple/pacifier (Blass 1991 A; Herschel 1998; Kaufman 2002; Stang 1997; Zahorodny 1999) thus providing the opportunity for non-nutritive sucking. In one trial (Herschel 1998), the sucrose group had a nipple (and the opportunity for non-nutritive sucking throughout the circumcision procedure), while the no treatment control group did not receive a pacifier at all. In two studies, the sugar solution was delivered using oral syringes (Kass 2001; Zolnoski 1993). In one trial, the method of delivery was not specified (Zahorodny 1998).

- Oral analgesics

Acetaminophen

Two trials compared acetaminophen to placebo with a total of 104 patients (Howard 1994; Macke 2001). The studies employed two different pain scales, and the results were not combined because the measures are not similar in conceptual development or measurement technique. Howard 1994 used a comfort score that measures 10 behaviours (sleep, facial expression, motor activity, tone, etc.) to arrive at a composite score of 0 to 20. The lower the score, the more uncomfortable the infant. Macke 2001 used the Nursing Child Assessment Feeding Scale (NCAFS) which measures mother-infant feeding interactions using 76 behavioral items based on the concepts of synchronism and adaptation. Lower scores on the NCAFS indicate less positive responses on the part of the infant. Results using the post-operative comfort score were not significant, but the total infant scores on the NCAFS were significant and favoured acetaminophen [MD 4.0, 95% CI 1.0 to 7.1; Metagraph 06.01]. All other outcomes (cry time, heart rate, respiratory rate Metagraphs 06.02, 06.03, 06.04) were not statistically significant.

ACTIVE VERSUS ACTIVE TREATMENT COMPARISONS

- DPNB versus EMLA

Three studies compared DPNB to EMLA for a total of 133 patients (Butler O'Hara 1998; Howard 1999; Lander 1997). Two studies measured different pain scores (Metagraph 07.01). The results were not combined because of conceptual and measurement differences between the scales. The Neonatal Infant Pain Scale (NIPS) consists of 6 behavioral components with a composite score of 0 to 6 based on facial expression, crying, breathing pattern, body movement and arousal. The behavioral distress score measures crying on a scale of 0 (no crying) to 3 (sustained crying). Lower scores indicate less pain for both measures. Results using both scales were statistically significant and favoured DPNB; NIPS [MD -2.5, 95% CI -3.3 to -1.7]; behavioral distress score [MD -0.3, 95% CI -0.5 to -0.03].

Cry time was measured in a single study and was not significantly different [MD -10%, 95% CI -30 to 10; Metagraph 07.02]. Heart rate was significantly reduced for the DPNB group [WMD -17 bpm, 95% CI -23 to -11; Metagraph 07.03] but heterogeneity was large (I2=93%). The random effects estimate was not statistically significant. Butler O'Hara 1998 had a large mean difference [MD -40 bpm, 95% CI -51 to -29]; when this study was removed, heterogeneity was absent and the overall fixed effects WMD was no longer significant [WMD -7 bpm, 95% CI -14 to 0.5]. The large heterogeneity may be related to differences in the characteristics of the study subjects. Infants enrolled in the Butler O'Hara 1998 trial were born prematurely and hospitalised in the neonatal intensive care unit (NICU). Postnatal age was 3 - 105 days by the time of circumcision (but less than 28 days after reaching 40 weeks corrected gestational age). Exposure to invasive treatments during their NICU stay may have caused the infants to become sensitized and thus respond differently than infants in the other two trials who were healthy newborns in the first few days of life. Respiratory rate (Metagraph 07.05), measured by a single study, was not significantly different.

- DPNB versus sucrose

Two trials compared DPNB to sucrose for 126 patients. In one trial, pain was measured using the modified behavioral pain scale (MPBS) (Kass 2001) and the results significantly favoured DPNB [MD -3.2, 95% CI -4.7 to -1.8; Metagraph 08.01]. Cry time was measured in one trial and significantly favoured the DPNB group [MD -166 s, 95% CI -211 to -121; Metagraph 08.02]. Heart rate also significantly favoured DPNB [WMD -27 bpm, 95% CI -33 to -20; Metagraph 08.03]. Heterogeneity was large (I2=94%) however, both trials measuring heart rate favoured the DPNB group. The effect on oxygen saturation (Metagraph 08.04) was not significant, heterogeneity was large (I2=96%), and the individual trial estimates were not consistent in direction of effect. The authors of one study (Herschel 1998) reported that a significant amount of oxygen saturation data (measured using pulse oximetry) was lost due to excessive motion. Also of note, the dose and delivery method of the sugar solution differed between the two studies. In one study (Kass 2001) subjects received 2 ml of 50% dextrose by oral syringe. In the other (Herschel 1998), subjects received up to 10 ml of 50% sucrose by nipple and had a pacifier throughout the procedure.

- DPNB versus ring block

One trial compared DPNB to ring block (Lander 1997) and included 27 patients. Results for cry time and heart rate were not significantly different between the groups (Metagraphs 09.01, 09.02).

- DPNB versus local block

A single trial compared DPNB to local block using 1% lidocaine (Masciello 1990) and included 20 patients. Local block was performed by injecting lidocaine subcutaneously into the foreskin at the 10 and 2 o'clock positions at the level of the corona. Results for serum cortisol significantly favoured the local block administration group [MD 306 nmol/dL, 95% CI 141 to 471; Metagraph 10.01].

- Ring block versus EMLA

Ring block was compared to EMLA in a single trial that included 28 patients (Lander 1997). Results for heart rate [MD -3 bpm, 95% CI -20 to 14; Metagraph 11.01] and cry time [MD -16 %, CI -36 to 3; Metagraph 11.02] were not significantly different between the groups.

- Buffered lidocaine DPNB versus lidocaine DPNB

Two trials compared buffered lidocaine DPNB to lidocaine DPNB and included 234 patients (Newton 1999; Stang 1997). In clinical trials with adult subjects, buffering lidocaine with sodium bicarbonate had shown potential to decrease the burning sensation of injection, and enhance the speed of anaesthesia. The results for all outcomes measured (behavioral distress score, cry time, heart rate, oxygen saturation and serum cortisol; Metagraphs 12.01, 12.02, 12.03, 12.04, 12.05) were not significantly different between the groups.

- EMLA versus topical lidocaine

One trial compared EMLA to 30% topical lidocaine, and included 40 patients (Woodman 1999). Cry time and oxygen saturation (Metagraphs 13.01, 13.03) were not significantly different. Heart rate was significant and favoured EMLA [MD -12 bpm, 95% CI -19 to -4; Metagraph 13.02].

- EMLA versus sucrose

Two studies (Mohan 1998; Zahorodny 1998) compared EMLA to sucrose (67 patients). Cry time, heart rate, oxygen saturation (Metagraphs 14.01, 14.02, 14.03) were not significant. Systolic and diastolic blood pressures mean differences could not be calculated because no standard deviations were provided (Metagraphs 14.04, 14.05), but both means were larger in the sucrose group, indicating higher mean blood pressure.

- EMLA versus music

A small pilot study (Joyce 2001) compared EMLA to music, and included 12 patients. None of the outcome results (cry time, heart rate, oxygen saturation, respiratory rate; Metagraphs 15.01, 15.02, 15.03, 15.04) were significantly different.

ENVIRONMENTAL COMPARISONS

- Music versus no treatment

Three studies compared the provision of music or other soothing sounds during the circumcision procedure (Joyce 2001; Marchette 1989; Marchette 1991). In one trial that included 12 patients (Joyce 2001) the effect of the intervention on the outcomes of cry time, heart rate, oxygen saturation and respiratory rate (Metagraphs 16.01, 16.02, 16.03, 16.04) was not significant. In a second study, music was compared with intrauterine sounds and no treatment (Marchette 1989). Although 103 infants were randomised, 45 records were deleted from analysis due to missing data or prolonged circumcisions related to physician training. The researchers did not report standard deviations, but they did report that during all steps of the circumcision procedure in which infants were touched with surgical instruments the interventions did not offset pain as indicated by heart rate, systolic blood pressure, facial expression, and behavioral state outcomes. In the third study (Marchette 1991) 121 infants were randomised to six groups and received either classical music, intrauterine sounds, a pacifier, music and a pacifier, intrauterine sounds and a pacifier, or no treatment. The researchers did not report means and standard deviations but they did state that the interventions tested did not greatly reduce circumcision pain as assessed by heart rate, blood pressure, transcutaneous oxygen saturation, and time crying.

COMPLICATIONS/ADVERSE EFFECTS

Ten studies reported adverse effects (see Additional Tables - Table 08). Adverse effects including gagging, choking, and emesis were reported in untreated groups, while DPNB groups exhibited minor bleeding, swelling and hematoma at the block injection site post-circumcision. EMLA use was associated with erythema and minor skin pallor. In one study (Holliday 1999), two subjects who received EMLA had redness and blistering of the foreskin, leading to closure of the EMLA arm of the study. Methaemoglobin levels were measured in two trials of EMLA and found to be within normal limits (Lander 1997; Taddio 1997). All adverse effects of pain interventions were reported to be transient in nature and were not considered serious. Several authors reported on the questionable clinical utility of topical anaesthetic interventions (Herschel 1998; Howard 1999; Lander 1997) given the dexterity required to apply the creams properly and the lengthy application time.

SUBGROUP AND SENSITIVITY ANALYSES

We examined two subgroups: length of wait time after penile block interventions (a priori) and choice of clamp for all procedures (post-hoc) on the most frequently reported outcome heart rate. One study compared different lengths of wait time and two anaesthetics (Spencer 1992) but did not report means and SDs. The authors did report that DPNB groups that received either anaesthetic exhibited decreased pain responses compared to the control group. We made indirect (or between study) comparisons. Six trials comparing DPNB to no treatment prescribed and reported wait times. The trials with the longer wait time (>5 minutes) did not perform significantly better than short wait time trials (</=5 minutes) [Metagraph 01.04]. In fact, the probability under the null hypothesis was close to significant (P=0.09 vs P=0.65) when Maxwell 1987 was removed and favoured shorter wait times. A similar and statistically significant result was calculated when comparing wait times in DPNB vs EMLA (P=0.04; Metagraph 07.04). Using an indirect comparison, the Mogen clamp trial performed significantly better on reducing heart rate compared to the Gomco clamp trials when Maxwell 1987 was again removed (P=0.05 vs P=0.07) under the DPNB versus no treatment comparison (Metagraph 01.05). Sucrose dose (a priori) was not analysed because there were too few studies under the same comparison and not enough information was provided.

Post-hoc, we considered two other potential treatment effect size modifiers: control intervention and choice of pacifiers. For ethical considerations, use of saline DPNB in pain research was generally abandoned since the early 1990's. Among the included studies for this review, three used both saline DPNB treatment (sham) and no treatment control arms (Arnett 1990, Holve 1983, Stang 1988 A). In one study saline DPNB was used to blind comparison of lidocaine DPNB with another active intervention (Howard 1999). The researchers wanted to control for the effects of the injection and fluid volume compression on penile sensation. None of the studies found statistical differences between these control arms. In our review, the two control arms were displayed separately in the metagraphs when the data were reported separately in the referenced study (Stang 1988 A). Visually, we also see no difference. Other concerns for blinding involve placebo creams. One study (Mohan 1998) did not use a placebo cream and one study (Benini 1993) reported using petroleum jelly as a placebo for EMLA cream.

In nine trials pacifiers were made available to all patients (Butler O'Hara 1998; Holliday 1999; Howard 1994; Howard 1999; Kurtis 1999 A; Mohan 1998; Spencer 1992; Stang 1988 A; Stang 1997). In one (Butler O'Hara 1998) all infants were provided with sugar pacifiers although sucrose was not the intervention under study and its use may have affected results obtained on outcome measures. In another (Herschel 1998) only one out of the three study groups received a pacifier because it was used to deliver a sucrose intervention. At least two studies (Kass 2001; Zolnoski 1993) strictly prohibited the use of pacifiers and used oral syringes to deliver the sucrose intervention. The remaining studies did not report pacifier use. There were too few studies to compare within outcomes, and we could not identify obvious deviations with use or non-use of pacifiers. Of mention, Blass 1991 A and Zahorodny 1999 both found that in a water via pacifier group, cry time was significantly reduced compared with the no treatment control group (P<0.001; P<0.001).

DISCUSSION

This systematic review incorporates data from 35 trials enrolling 1952 neonates to examine a variety of interventions for circumcision pain relief. Although the results are generally applicable to current practice, the review identified a number of important limitations of the primary studies included in the review and thus the results should be interpreted with some caution. Sample size in the majority of the trials was small (total sample size was < or = to 80 in 32 out of 35 trials), and there were some differences in the characteristics of the study subjects. Butler O'Hara 1998 enrolled neonates from an NICU that were between 3 and 105 days postnatal age at the time of circumcision (although still less than 28 days after reaching 40 weeks corrected gestational age). Holliday 1999 enrolled low birthweight neonates aged 25 - 27 days at circumcision. Each of these groups of subjects could have experienced numerous painful or invasive treatments during their stay in NICU prior to circumcision. Accordingly, their responses during circumcision, regardless of the intervention, could have been different from those of the healthy newborns that were recruited for the remainder of the trials.

All of the studies included in this review were described as randomised, but 15 of the trial reports did not include sufficient information or describe adequate procedures for assurance of blinding of randomisation. Nine of the trials were double-blind for all interventions, but some interventions such as block technique could not be blinded. In six trials of DPNB, a standardized approach to the circumcision procedure was not described in the reports, making it impossible to tell whether every infant underwent exactly the same surgical process. The impact of this could be intensified within individual trials where more than one operator performed the circumcisions (e.g. Howard 1999, Macke 2001). Other differences that may have affected outcome results between trials of the same comparison include the variability in wait time after block administration, length of fasting prior to circumcision, provision of pacifiers or other non-study interventions, and use of different surgical clamps. Finally, differences between trials in the structure of pain interventions were evident, especially in trials of oral sucrose where the dose and method of delivery varied substantially.

The studies included in this review reported on measurement of a variety of pain outcomes (physiological, behavioral, biochemical). Techniques and methods for measurement of outcomes were more dissimilar than similar across the trials, even within a single outcome variable (e.g. heart rate), and this presented significant challenges to combining outcome results. In particular, the dissimilarity in outcome measures severely limited the feasibility of combining pain scores across the included studies. None of the reports included in this review offered a definition of pain, and in general, the reports did not differentiate between the painful versus the distressing/stressful aspects of the circumcision procedure (e.g. removal of foreskin versus application of restraints). Reasons for selection of pain scores as outcome measures were not articulated in most cases, and among the included studies, a variety were used that differed in conceptual development and in measurement technique. Some pain scores were author-devised measures with no reported psychometric testing (Arnett 1990; Holliday 1999; Weatherstone 1993), while others measured behavioral indicators that were not conceptually linked to the neonate's experience of pain (Dixon 1984; Macke 2001; Newton 1999; Stang 1988 A). Others were subjective in their measurement technique (Howard 1999; Stang 1997). In six trials, researchers employed validated pain scales developed specifically to measure neonatal pain (Benini 1993; Butler O'Hara 1998; Howard 1994; Joyce 2001; Kass 2001; Taddio 1997).

Sixteen trials included in this review either did not report outcome data, or did not report data in a format that could be analysed in this review. One of the strengths of this review was that we were able to obtain additional information for three trials. Where means and standard deviations were not available, data were imputed or derived from graphs contained in the reports, and missing standard deviations were either calculated from other summary statistics or substituted with singular or mean standard deviations from similar trials allowing us to maximize the data included under each comparison.

DPNB was identified as the most effective intervention and demonstrated decreases in time crying and heart rate that were statistically and clinically significant (time crying 54% less, heart rate 30 beats per minute less) when compared with placebo or no treatment. EMLA also reduced pain responses when compared with placebo but the differences in time crying (15% less) and heart rate (15 beats per minutes less) were not as large as those observed with DPNB. Topical lidocaine demonstrated statistically significant decreases in time crying (60 seconds less), heart rate (9 beats per minute less) and serum B-endorphin levels (49 pg/ml less) compared to placebo. The issue of the statistical versus clinical significance of the outcome results was not discussed in any of the study reports, and no author identified a threshold for clinically significant (as opposed to statistically significant) intervention effects. It should be emphasized that none of the interventions examined in these trials completely eliminated pain responses to circumcision.

Ease of administration of the pain interventions will influence the applicability of the results of this review to current clinical practice. The relative ease of establishing the different penile blocks was not systematically evaluated, but it was suggested that the ring block technique is easier and safer because it eliminates the risk of injection of lidocaine into the dorsal vessels (Hardwick Smith 1998). A single study reported on use of local penile block (Masciello 1990) which appears to be similar in technique to ring block. Few adverse effects were reported with use of any of the penile blocks. EMLA and lidocaine topical anaesthetics are effective for circumcision pain when compared with placebo or no treatment, but their use may be precluded because of difficulties in application and the time required for maximum anaesthetic effect. Adverse effects such as transient skin reactions were reported but not considered serious, and methaemoglobin levels, when measured, were within normal range.

AUTHORS' CONCLUSIONS

Implications for practice

Circumcision is a painful procedure and routine or elective newborn circumcision is not recommended by either the American Academy of Pediatrics or the Canadian Paediatric Society. However, if circumcision is performed, the results of this review show that DPNB, RB and the topical anaesthetics EMLA and lidocaine cream can be recommended over no treatment for attenuation of circumcision pain. DPNB demonstrated the most consistent results, has been the most comprehensively studied, and was the most effective in terms of clinically significant reductions in pain responses. RB is also effective to reduce circumcision pain compared with placebo. The RB technique may be easier and safer to use because it eliminates the risk of injection of lidocaine into the dorsal vessels.

EMLA and lidocaine topical anaesthetics are effective for circumcision pain when compared with placebo or no treatment, but their use may be precluded because of difficulties in application and the time required for maximum anaesthetic effect. Adverse effects with EMLA use such as transient skin reactions were reported but not considered serious, and methaemoglobin levels, when measured, were within normal range. Topical anaesthetics are a less effective alternative to no treatment when expertise with penile blocks is not readily available.

Results for oral sucrose, oral analgesics and environmental modification interventions were either inconsistent or did not produce significantly different outcome results. These therapies cannot be recommended as treatments for circumcision pain.

None of the studied interventions completely eliminated the pain response to circumcision.

Circumcisions performed using the Mogen clamp take less time than is required using Gomco clamps. Shorter procedure time may reduce the total amount of pain experienced during circumcision, and may be important in terms of practitioner time to do the surgery.

Implications for research

Future studies should compare two or more active interventions for pain relief - a placebo or no-treatment control group is no longer acceptable. The impact of different "wait times" on the effectiveness of penile blocks and the relative acceptability and ease of administration of DPNB versus RB for practitioners should be systematically investigated. Use of the Mogen clamp in combination DPNB and RB should be investigated further to identify an optimal target time for circumcision surgery and to maximize anaesthetic effect. Although sucrose cannot be recommended as an intervention for circumcision pain at this time, research to determine the optimal dose and delivery method and the effect of combining oral sucrose with other interventions and comfort measures (e.g. nonnutritive sucking) should be pursued.

Lidocaine block and topical anaesthetic interventions could be useful in other situations where neonates undergo acute procedural pain. The pain associated with chest tube insertion, lumbar puncture, insertion of percutaneous central lines and other procedures commonly performed on high risk neonates may be significantly reduced with use of an appropriately adapted lidocaine block technique or topical anaesthetics. Further research should be pursued to identify situations where this potential can be examined.

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POTENTIAL CONFLICT OF INTEREST

Two of the reviewers, Brady-Fryer and Lander, were authors of a trial, Lander 1997, included in this review.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Arnett 1990**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	52 male NB; FT; BW > 2000 g; 5 min Apgar scores >/= 6
Interventions	0.4 ml lidocaine DPNB (n=23) 0.4 ml saline DPNB (n=22) no treatment control (n=7)

Characteristics of included studies (*Continued*)

	WT not reported; mean length for entire procedure was 4.4 minutes
Outcomes	HR, infant irritability, O2sat
Notes	- no treatment control group added after study start; results for saline DPNB group and no treatment group were combined for analysis (n=29) - data missing for 3 subjects (1 in each group) and cases deleted from analysis - procedure not standardized - lower dose lidocaine used (0.4 ml total) - subjects fasted 90 minutes prior to circumcision - Gomco clamp - adverse effects reported
Allocation concealment	A

Study	**Benini 1993**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - yes
Participants	28 male NB; FT; BW > 2500g; 5 min Apgar > 7; < 7 d age
Interventions	0.5 ml (0.5g) LP cream (n=14) 0.5 ml (0.5 g) petroleum jelly (n=13) applied and covered with occlusive dressing 45 - 60 min prior
Outcomes	HR, O2sat, % time crying, facial action
Notes	- 1 withdrawal from placebo group because infant not FT - procedure standardized to 9 phases - Gomco clamp - no adverse effects reported
Allocation concealment	B

Study	**Blass 1991 A**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - yes
Participants	30 male NB, FT; 28 - 54 h age; Apgars > 8
Interventions	1.5 ml 24% sucrose by nipple 1.5 ml water by nipple no treatment control *comparison is sucrose versus water (placebo) number subjects per group not specified 3 min WT after intervention
Outcomes	% time crying
Notes	- assumed distribution was equal (10/group) for data analysis - procedure not standardized - infants fasted for at least 1 hr prior - Gomco clamp
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Blass 1991 B**
Methods	see Blass A
Participants	see Blass A
Interventions	* comparison is sucrose versus no treatment
Outcomes	
Notes	
Allocation concealment	B

Study	**Butler O'Hara 1998**
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - yes
Participants	50 male infants in NICU; >/= 34.5 weeks (post-menstrual) at time of circumcision and stable for discharge participants were 3 -105 days age at time of circumcision
Interventions	0.5 ml (0.5g) LP cream (n=21) 0.7 - 1.0 ml lidocaine DPNB + placebo cream (n=23) creams applied 60 min prior and covered with occlusive dressing 3 min WT after DPNB
Outcomes	HR; RR; NIPS score (primary outcome)
Notes	- non-randomized, no treatment group (n=20) also had data collected - outcome data for 6 subjects (4 LP cream, 2 DPNB) lost due to technical difficulties - infants fasted for 2 to 3 hours before circumcision - all subjects had sugar pacifiers during procedure - procedure standardized - Plastibell clamp - adverse effects reported
Allocation concealment	A

Study	**Dixon 1984**
Methods	RCT Blinding of randomization - yes Blinding of intervention - can't tell Complete follow-up - yes Blinding of outcome measurement - partial
Participants	31 male NB, FT, AGA, < 7 days age, > 2500 gm, 5 min Apgar > 7
Interventions	0.8 ml lidocaine DPNB (n=15) 0.8 ml saline DPNB (n=8) no treatment control (n=8) 4 - 5 min WT
Outcomes	Brazelton Neonatal Assessment Scale
Notes	- Holve 1983 is primary study report - circumcision procedure not standardized - all circumcisions performed by single physician - Gomco clamp - adverse effects reported
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	Hardwick Smith 1998
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - can't tell Blinding of outcome measurement - no
Participants	40 male NB; FT; Apgar >/= 7; 6 hr - 5 days age; fasting 30 -120 min prior; normal exam
Interventions	1.0 ml 5% lidocaine RB (n=20) no treatment control (n=20) 3 min WT
Outcomes	HR; RR; O2sat; behavioral state; cry time
Notes	- O2sat not recorded in up to 50% of infants - single operator performed all circumcisions - Gomco clamp - no adverse effects reported
Allocation concealment	A

Study	Herschel 1998
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - yes
Participants	120 male NB; FT; > 2500g; Apgar >/= 8 at 5 min; >/= 12 hr age
Interventions	0.8 ml 1% lidocaine DPNB (n=40) 10 ml 50% oral sucrose via nipple (n=39) no treatment control (n=40) 3 min WT for DPNB; 2 min WT for sucrose group
Outcomes	HR; O2sat (%)
Notes	- 1 withdrawal from sucrose group, circumcision contraindicated - O2 sat data missing - 31% intervals control, 10% intervals DPNB, 8% sucrose - infants fasted 30 min prior to circumcision - sucrose group had nipple throughout procedure, other groups did not have pacifier - Gomco clamp
Allocation concealment	A

Study	Holliday 1999
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	50 male preterm/low birthweight NICU patients, subjects weighed 1600 to 2500g at time of circumcision 25-27 days age, 36 week GA at circumcision
Interventions	0.8 ml 1% lidocaine DPNB + placebo cream (n= 19) LP cream (n=12) (group enrollment stopped, excluded from data analyses) placebo cream (n=19)

Characteristics of included studies (*Continued*)

	DPNB 5 min WT cream applied 1 hr prior and covered with occlusive dressing
Outcomes	HR, RR, O2sat, systolic BP, behavioral score, serum B-endorphin
Notes	- LP cream group discontinued due to redness and blistering of foreskin in 2 infants - procedure not standardized - all circumcisions performed by single operator - pacifiers provided - Gomco clamp - no adverse effects reported for DPNB group
Allocation concealment	A

Study	**Holve 1983**
Methods	RCT Blinding of randomization - yes Blinding of intervention - partial Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	31 male NB; FT, < 7 days age, > 2500 gm, 5 min Apgar > 7
Interventions	0.8 ml 1% lidocaine DPNB (n=15) 0.8 ml saline DPNB (n=8) no treatment control (n=8) 4-5 min WT
Outcomes	HR; % time crying per interval; clinical observation of anesthesia effectiveness (good, fair, poor)
Notes	- procedure standardized - Gomco clamp - adverse effects reported
Allocation concealment	A

Study	**Howard 1994**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	44 male NB, healthy, AGA, FT, Apgars > 7, >/= 24 h age
Interventions	acetaminophen 15 mg/kg/dose (n= 23) placebo (n= 21) given 2 hr prior and q 6H X 24 hr following
Outcomes	HR; RR; cry time; post-operative comfort score; feeding behavior pre/post
Notes	- infants fasted 2 - 3 h prior to circumcision - all had pacifiers - procedure standardized - single operator performed all circumcisions - Gomco clamp - no adverse effects reported
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	**Howard 1999**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - unclear Blinding of outcome measurement - yes
Participants	62 male NB; healthy; AGA; FT
Interventions	1g LP cream + 0.8 ml saline DPNB (n=31) 0.8 ml 1% lidocaine DPNB + 1g placebo cream (n=29) 4 min WT for DPNB creams applied 1 hr prior and covered with occlusive dressing
Outcomes	HR; RR; behavioral distress score
Notes	- 2 infants withdrawn (1 tachypnea, 1 parents withdrew consent) - procedure standardized - 3 operators performed the circumcisions - all subjects had pacifiers - Gomco clamp - no adverse effects reported
Allocation concealment	A

Study	**Joyce 2001**
Methods	RCT; Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	23 male NB, FT; 5 min Apgar > 7; BW > 2500 g; age < 7 d
Interventions	LP cream (1 - 2 g) + music (n=6) LP cream + no music (n=5) placebo cream + music (n=7) placebo cream + no music (n=5) cream applied 1 hr prior and covered with occlusive dressing music started just prior to procedure and continued to 10 min post procedure
Outcomes	HR, O2sat, cry duration; RR, Riley Infant pain scale, salivary cortisol, infant state
Notes	- pilot study - no adverse effects reported
Allocation concealment	A

Study	**Kass 2001**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	71 healthy male NB
Interventions	lidocaine DPNB (n=24) 2ml D50W orally (n=23)

Characteristics of included studies (*Continued*)

	2 ml H2O orally (n=24) WT 2 to 6 min
Outcomes	time cry (primary outcome); HR; O2sat ; modified behavioral pain scale
Notes	- additional data obtained from authors - no pacifiers used - Gomco clamp
Allocation concealment	B

Study	**Kaufman 2002**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	57 NB; healthy; male; FT; Apgar > 7 at 5 min
Interventions	Mogen + water pacifier (15) Mogen + 24% sucrose pacifier (n=14) Gomco+ water pacifier (n=14) Gomco + 24% sucrose pacifier (n=14)
Outcomes	time crying; grimacing, procedure length
Notes	- all subjects had EMLA cream applied between 1 and 3 hr before procedure - single operator performed all circumcisions -procedure standardized - infants fasted from 15 min to 4 hr before procedure - no adverse effects reported
Allocation concealment	B

Study	**Kurtis 1999 A**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	48 male NB; FT; 5 min Apgar >/= 7
Interventions	Mogen clamp and 0.8 ml 1% lidocaine DPNB (n=16) Mogen clamp and no DPNB (n=16) Gomco clamp and 0.8 mL 1% lidocaine DPNB (n=8) Gomco clamp and no DPNB (n=8) 5 minute WT
Outcomes	time crying, HR, O2sat, salivary cortisol, RR
Notes	- all subjects had pacifiers - infants fasted 1 - 2 hr before procedure - Mogen = 8 procedural steps; Gomco = 13 procedural steps
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Kurtis 1999 B**
Methods	see Kurtis 1999 A
Participants	see Kurtis 1999 A
Interventions	comparison is Mogen versus Gomco for patients receiving no DPNB
Outcomes	
Notes	
Allocation concealment	D

Study	**Lander 1997**
Methods	RCT Blinding of randomization - yes Blinding of intervention - partial Complete follow-up - no Blinding of outcome measurement - yes
Participants	52 male NB; FT; AGA; 1-3 d age
Interventions	2g LP cream (n=15) placebo cream (n=12) 0.8 ml 1% lidocaine DPNB (n=14) 0.8 ml 1% lidocaine RB (n=13) - penile blocks 8 min WT; creams applied 90 min prior and covered with occlusive dressing
Outcomes	HR; time cry; O2 sat, RR, palmar sweat, metHgb level
Notes	- 2 withdrawals, 1 in placebo group, 1 in RB group (1 parents unable to remain in hospital, 1 required phototherapy) - procedure standardized - Gomco clamp - adverse effects reported
Allocation concealment	A

Study	**Macke 2001**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	60 male NB; FT; Apgar >/= 8
Interventions	acetaminophen 10 mg/kg (n=29) placebo (n=31) given 1 hr prior to circumcision
Outcomes	HR , Nursing Child Assessment Feeding Scale, cry time, infant state
Notes	- 12 operators performed circumcisions in analgesia group, 21 performed circumcisions in placebo group - Gomco clamp
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	Marchette 1989
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	58 male NB; Apgar >/= 8
Interventions	classical music (n=25) intrauterine sounds (n=15) control (no nurse present) (n=18)
Outcomes	HR; heart rhythm; BP; TcpO2; MDFMCS; BNAS
Notes	- 103 subjects randomized, 45 cases deleted due to missing data or prolonged circumcisions - procedure standardized - Gomco clamp
Allocation concealment	B

Study	Marchette 1991
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	121 male NB; Apgar =/> 6; normal delivery; 2 - 9 days age
Interventions	taped music (n=20) intrauterine sounds (n=20) pacifier (n=20) music and pacifier (n=20) intrauterine sounds and pacifier (n=20) control - no treatment (n=21)
Outcomes	HR, rhythm, BP; tcPO2; rate pressure product, BNAS; crying
Notes	- cases excluded if circumcision longer than 15 min or if bleeding - Gomco clamp
Allocation concealment	B

Study	Masciello 1990
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	30 male NB, healthy, FT
Interventions	0.8 ml 1% lidocaine DPNB (n=10) 0.8 ml 1% lidocaine local block (n=10) no treatment control (n=10) 5 min WT
Outcomes	plasma cortisol, HR, O2sat, cry

Characteristics of included studies (*Continued*)

Notes	- cortisol levels obtained for first 3 cases lost (1 in each group) - all fasted for at least 3 hours prior - procedure standardized - single operator performed all circumcisions - Gomco clamp
Allocation concealment	B

Study	**Maxwell 1987**
Methods	RCT; Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	30 male NB; FT; healthy
Interventions	0.8 ml 1% lidocaine DPNB (n=20) no treatment control (n=10) 5 min WT
Outcomes	HR, O2sat, BP, plasma lidocaine
Notes	- subjects fasted for 2 hr prior - procedure not standardized - Gomco clamp - no adverse effects observed
Allocation concealment	A

Study	**Mohan 1998**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	60 male NB; FT; BW>/= 2500 g; 5 min Apgar >/= 7; < 5 days age
Interventions	5 g LP cream + 2 ml 24% sucrose via pacifier (n=19) 5 g LP cream + water via pacifier (n=20) 2 ml 24% sucrose via pacifier (n=21) water via pacifier (n=19) - non-randomized control - cream applied 45-60 min prior, covered with occlusive dressing
Outcomes	HR; O2sat; BP; cry duration
Notes	- control group not randomized - all received pacifiers - procedure standardized - Gomco clamp - no adverse effects reported
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Mudge 1989**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	44 male NB; 5 min Apgar > 7; BW 2.5 - 4.5 kg; FT; age 12 - 72 h
Interventions	4% lidocaine cream (n=20) placebo cream (n=24) cream applied 2 hr prior covered with occlusive dressing
Outcomes	HR, RR, O2sat, cry time, behavior
Notes	- Gomco clamp - procedure standardized
Allocation concealment	A

Study	**Newton 1999**
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	194 male NB; healthy
Interventions	0.8 ml 1% lidocaine DPNB (n=92) 0.8 ml 1% buffered lidocaine (n=102)
Outcomes	HR (primary outcome variable); O2sat; number crying/phase; modified BNAS
Notes	- complete data on crying for 165 subjects; complete data on BNAS for 194 - complete data on HR, O2 sat for 143 subjects due to technical difficulties - procedure standardized - Mogen clamp - adverse effects reported
Allocation concealment	A

Study	**Spencer 1992**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	75 male NB; BW 2500 - 4500 g; >12 hr age; 5 min Apgar > 6; normal exam
Interventions	lidocaine DPNB - 5 min WT (n=15) lidocaine DPNB with 2 min WT (n=15) 1% chloroprocaine DPNB with 3 min WT (n=15) 1% chloroprocaine DPNB with 5 min WT (n=15) no treatment control (n=15)
Outcomes	cry duration, O2Sat, HR, BNAS

Characteristics of included studies (*Continued*)

Notes	- all received pacifiers - fed 60 to 90 min prior to circumcision - procedure standardized - Gomco clamp
Allocation concealment	B

Study	**Stang 1988 A**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	60 male NB; > 24 hr age; BW > 3000 g; 5 min Apgar > 7; uncomplicated delivery
Interventions	0.8 ml 1% lidocaine DPNB (n=20) saline DPNB (n=20) no treatment control (n=20) 5 min WT *comparison is DPNB versus no treatment
Outcomes	% time cry, modal behavior state, plasma cortisol
Notes	- all handling avoided for 2 hr prior - 1/2 had blood sample for cortisol at 30 min, 1/2 at 90 min - all received pacifiers and continuously soothed - procedure standardized to 3 periods - Gomco and Plastibell used at operator's discretion - adverse effects reported
Allocation concealment	B

Study	**Stang 1988 B**
Methods	see Stang A
Participants	see Stang A
Interventions	*comparison is DPNB versus sham (saline) treatment
Outcomes	see Stang A
Notes	see Stang A
Allocation concealment	B

Study	**Stang 1997**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	80 male NB, > 20 hr age; BW 3000 - 4000 gm; 5 min Apgar >/= 8; FT
Interventions	group 1 = 0.8 ml 1% lidocaine DPNB, padded restraint , water via pacifier (n=20) group 2 = 0.8 ml 1% lidocaine DPNB, regular restraint, 24% sucrose via pacifier (n=20) group 3 = 0.8 ml 1% buffered lidocaine DPNB, regular restraint, water via pacifier (n=20) group 4 = 0.8 ml 1% lidocaine DPNB, regular restraint, water via pacifier (n=20) (control)

Characteristics of included studies (*Continued*)

	5 min WT
Outcomes	behavioral distress scale, plasma cortisol 30 min post-circ
Notes	- 5th arm of study (24% sucrose only) abandoned due to high behavioral distress scores - no forced preoperative fasting period - all handling avoided for 1 hr prior - procedure standardized - all given pacifiers - Gomco and Plastibell methods used
Allocation concealment	B

Study	**Taddio 1997**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - yes Complete follow-up - no Blinding of outcome measurement - yes
Participants	68 male NB, BW >/= 2500 g; FT; no jaundice or metHgb
Interventions	1 g (1ml) LP cream (n=29) 1 g (1ml) placebo cream (n=30) creams covered with occlusive dressing for 60 - 80 min prior
Outcomes	HR, time cry, NFCS, systolic/diastolic BP, metHgb
Notes	- 68 subjects randomized, 8 in the LP group included in safety analysis only, 59 subjects in the efficacy analysis - procedure standardized - Gomco clamp - adverse effects reported
Allocation concealment	B

Study	**Weatherstone 1993**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	30 male NB; BW >/= 2500 g; FT; Apgar >/= 7; 6-72 hr age
Interventions	0.5 g 30% lidocaine cream (n=15) placebo cream (n=15) applied 20 min prior to circumcision and covered with occlusive dressing
Outcomes	HR, RR, O2 sat, BP, Newborn Pain Behavior Scale, serum B-endophin (15 min post), serum lidocaine
Notes	- procedure not standardized - Gomco and Plastibell clamps - no adverse effects reported
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	**Williamson 1983**
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	30 male NB; BW = 2500 - 4000 g; 24 - 72 hr age; FT; Apgar score > 7; systolic BP > 40 mm Hg
Interventions	0.6 to 0.8 1% ml lidocaine DPNB (n=20) no treatment control (n=10) 4 min WT
Outcomes	TcpO2, time cry; HR, RR
Notes	- fasted at least 2 hr prior - PI performed all circumcisions - Gomco clamp
Allocation concealment	C

Study	**Williamson 1986**
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	30 male NB; Apgar > 7; BW 2500 - 4500 g; FT; 24 - 72 hr age; normal physical exam
Interventions	lidocaine DPNB (n= 11) no treatment control (n=13) 5 min WT
Outcomes	plasma cortisol pre and 30 min post circumcision
Notes	- 6 additional infants circumcised after study completed to serve as controls for blood sampling/injections - all circumcisions done by PI - Gomco clamp
Allocation concealment	A

Study	**Williamson 1997**
Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - yes Blinding of outcome measurement - yes
Participants	30 male NB; FT; >/= 24 hr age; BW 2500- 4500g; Apgar > 7
Interventions	lidocaine DPNB (n=20) no treatment control (n=10)
Outcomes	TcPO2, RR, HR, cardiac rhythm, cry time and type
Notes	- procedure standardized - fasting at least 2 hr prior - Gomco clamp - adverse effects reported
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	**Woodman 1999**
Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	61 male NB; Apgar > 7; FT; BW > 2500 g; 6-72 hr age
Interventions	1 g (1 ml) LP cream (n=20) 30% lidocaine cream (n=20) placebo cream (n=21) creams applied 1 hr prior and covered with occlusive dressing
Outcomes	HR; time crying; O2sat
Notes	- all subjects fasted for at least 1 hr prior - procedure standardized - all circumcisions performed by same operator - Gomco clamp
Allocation concealment	A

Study	**Zahorodny 1998**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - yes Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	53 healthy male NB
Interventions	1g LP cream + 2 ml 50% sucrose 1g LP cream + 2 ml H2O 1g placebo cream + 2 ml 50% sucrose 1g placebo cream + 2mL H2O creams applied 1 hr prior; sucrose or H2O oral 2 min prior total n=53, allocation not clear
Outcomes	time cry
Notes	abstract only, number of subjects per group not reported assumed equal distribution to groups unable to obtain additional data
Allocation concealment	B

Study	**Zahorodny 1999**
Methods	RCT Blinding of randomization - can't tell Blinding of intervention - yes Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	61; healthy male NB
Interventions	10 ml 50% sucrose via pacifier 10 ml H2O via pacifier no treatment control total n=61, allocation not clear

Characteristics of included studies (*Continued*)

Outcomes	HR, time cry
Notes	abstract only, unable to obtain additional data assumed equal distribution to groups
Allocation concealment	B

Study	**Zolnoski 1993**
Methods	RCT Blinding of randomization - yes Blinding of intervention - can't tell Complete follow-up - yes Blinding of outcome measurement - yes
Participants	20 male NB, 8 - 120 hr age, FT; no maternal medication, BW > 2700 g, 5 min Apgar >/= 7
Interventions	2.4 ml 24% sucrose (n=10) 2.4 ml water via syringe (n=10) given 3 min prior
Outcomes	cry time, HR
Notes	- pilot study - Master's thesis - procedure standardized - Gomco clamp
Allocation concealment	A

Participant Characteristics: NB = newborn; AGA = growth appropriate for gestational age; BW = birthweight; FT = full-term >/= 37 weeks gestation; NICU - neonatal intensive care unit;

Interventions: DPNB = dorsal penile nerve block as described in Kirya (1978) using 1% lidocaine without epinephrine; RB = ring block following the procedure outlined by Broadman (1987); local block = local anesthesia performed by injecting 0.4 ml of 1% lidocaine without epinephrine subcutaneously into two positions on the foreskin at the level of the corona; LP cream = a lidocaine-prilocaine cream commonly known as EMLA (eutectic mixture of local anesthetics); D50W = 50% dextrose oral solution; control/no treatment group = group receiving no intervention for pain; placebo group = group receiving sham intervention which mimics active interventions; WT = the time from completion of administration of pain relief intervention to the start of circumcision procedure;

Scales: NIPS = Neonatal Infant Pain Scale consisting of six behavioral components with a composite score of 0 to 7 (Lawrence, 1993); NFCS score = evaluates the presence or absence of 10 discrete facial actions at outlined in Grunau (1987), scored from videotape in 2 sec intervals for the first 20 sec of each circumcision phase; BNAS = Brazelton Neonatal Behavioral Assessment Scale; MDFMCS = Maximally Discriminative Facial Movement Coding System for coding facial movements of three facial regions to determine emotions demonstrated; NCAFS = Nursing Child Assessment Feeding Scale measures mother-infant interaction using 76 behavioral items grouped into six subscales based on concepts of adaptation and synchronism - mother and infant are observed during natural feeding session; MBPS = modified behavioral pain scale;

Physiological measures: HR= heart rate in beats/minute (bpm); TcpO2 = transcutaneous oxygen saturation; O2sat = % oxygen saturation in the blood; BP = blood pressure; RR = respiratory rate in breaths/minute;

Biochemical measures: [PC] = plasma cortisol concentration; metHgb = methemoglobin

Characteristics of excluded studies

Malnory 2003	Study subjects not randomized to treatment groups, intervention chosen by physician
Mintz 1989	Not a clinical trial, no comparison between groups
Olson 1998	Study subjects not randomized to treatment groups, intervention chosen by physician
Russell 1996	Not a clinical trial, all subjects received EMLA, Plastibell technique
Taddio 2000	Cohort design with two study groups; all recruited subjects assigned to Group 1; Group 2 data obtained from previously conducted RCT

Characteristics of excluded studies (*Continued*)

Taeusch 2002	Trial of head to head comparison of surgical devices (clamps) used for circumcision procedure, procedural differences have indirect effect on circumcision pain

ADDITIONAL TABLES

Table 01 Trials assessing pain/behavior scores

Study ID	**scale**	**measurement method**	**data reported**	**data preparation**
Arnett 1990	infant irritability irritabilify graded subjectively on a scale of 1 to 6 with 1 representing the least crying/agitation and 6 the most	nurse and physician rating of infant irritability graded before, during and 1 hour after circumsion	mean/SD of assessment during procedure	data entered into meta-analysis as reported
Benini 1993	Neonatal Facial Action Coding System (Grunau , 1990b) 10 facial actions scored, 7 (brow bulge, eye squeeze, nasolabial furrow, open mouth, vertical stretching of mouth, horizontal stretching of mouth, taut tongue) entered into analysis	facial actions videotaped continuously, second by analysis of facial actions 10 facial actions scored, 7 facial actions entered into analysis total score computed by summing 7 categories	outcome data (means/SDs) obtained from authors	calculate arithmetic mean of scores across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [application of dorsal clamp, incision, adhesion lysis, Gomco clamp on, foreskin excision, Gomco clamp off, restraints removed]
Butler-O'Hara 1998	Neonatal Infant Pain Scale (NIPS) consists fo 6 behavioral components with a composite score of 0 to 6 5 components used - facial expression, cry, breathing pattern, arm movements, state of arousal (Lawrence, 1993)	procedure videotaped NIPS scores assigned for each of 6 events (clamping of foreskin, adhesion lysis, dorsal cut, adhesion lysis, tying of Plastibell, foreskin excision) mean NIPS score calculated for each infant	mean(SD) NIPS score/group	data entered into meta-analysis as reported
Dixon 1984 (Holve 1983 is primary study report)	Brazelton Neonatal Assessment Scale (BNAS) consists of 27 behavioral items, each scored on scale of 1 to 9, and 20 reflexes scored on 3	examinations conducted prior to (exam 1), following the circumcision (exam 2), and 1 day after circumcision (exam 3)	mean scores/item for 3 exam times	states "variation in item scores precluded determination of statistically significant differences between groups' not included in meta-

Table 01 Trials assessing pain/behavior scores (*Continued*)

Study ID	scale	measurement method	data reported	data preparation
	point scale scale examines organization and integration of behavior in response to positive and adversive situations			analysis
Hardwick-Smith 1998	behavioral state (Stang et al 1988) score 1 - 6 in order of increasing arousal	scored at baseline, 10 intervals during procedure, and 2 hr post-circumcision	p values	not included in meta-analysis
Holliday 1999	behavioral scale - includes 8 behavior state variables (sleep state, cry, facial expression, torso movement, soothability, response to distress, need for tactile stimulation, environmental noise) each variable scored 1 to 6, scores totaled for each infant	assessed 20 min before, during and after circumcision	means scores/group reported in graph format	graph extractions to obtain mean/SD
Howard 1994	Postoperative Comfort Score (Attia 1987) 10 behaviors, each scored 0, 1, or 2, possible scores 0 to 20, lower score = less comfortable	assessed baseline, and postcircumcision at 30, 60, 90, 120, 360 min	mean/SD scores/group/interval mean/SD change from baseline scores/group/interval	data entered into meta-analysis as reported for 30 min post-circumcision scores
Howard 1999	behavioral distress scale (from Stang et al 1997) score 0 - 3 based on Brazelton statte assessment score 0 = neutral to 3 = sustained cry	videotape of procedure assessed and scores assigned every 30 s of the procedure	mean/SE scores / group for stages 2 to 6 of procedure	data entered into meta-analysis as reported "procedure" = [block administration to recovery; includes 4 min WT and Gomco clamp left on for 5 min]
Joyce 2001	Riley Infant Pain Scale 6 categories of behavior (vocal, facial expression, body movement, sleep, consolability, response to touch) rates on scale of 0 (no pain) to 3 (severe pain)	videotape of procedure assessed at baseline, undressing, restraints, cleanse, clamping, cutting, end of procedure, 15 min post and 30 min post	RIPS score / group / phase presented in graphic format p values	not included in meta-analysis
Kass 2001	MBPS - modified	scored at 30 s intervals	mean/SD for baseline	mean/SD procedure

Table 01 Trials assessing pain/behavior scores (*Continued*)

Study ID	scale	measurement method	data reported	data preparation
	behavioral pain scale (Taddio et al, 1995) rates facial expression, crying, and body movements to obtain a score of 0 to 10		and procedure MBPS / group obtained from authors	scores entered into meta-analysis
Macke 2001	Nursing Child Assessment Feeding Scale (NCAFS) 76 behavioral binary items (yes,no) grouped into 6 subscales based on concepts of adaptation and synchronism	scored during feeding interaction before and after circumcision	mean/SD score pre/post circumcision	data included as reported
Newton 1999	Brazelton Neonatal Assessment Scale - scale categorized to 6 level\s - (deep sleep (1), light sleep (2) drowsy (3), quiet alert (4) active alert (5) crying (6) (Brazelton, 1984)	3 evaluations - baseline, injection, clamp application	modal state/group	data not included
Stang 1988	behavioral state 6 levels = quiet sleep (1), active sleep (2), drowsy (3), alert (4), active awake (5), crying (6) (Brazelton, 1973)	assessed at baseline, during injection, during circumcision, and 30 min from the start of the circumcision	modal response / group / time period	data not included
Stang 1997	behavioral state scale and behavioral distress scale 4 levels - neutral (0), minimal fuss (1), moderate fuss (2), sustained cry (3) (Brazelton, 1973)	behavioral state and distress scored every 30 s beginning 2 min before circumcision scores averaged for 5 periods - preinjection, injection, 2 min post-injection, 4 min post-injection, circumcision	mean/SD /group / study period	mean/SD for circumcision period included
Taddio 1997	Neonatal Facial Coding System (Grunau et al, 1987; 1990) codes presence or absence of 10 discrete facial actions (brow bulge, eye squeeze, nasolabial furrow, open mouth, vertical	facial actions continuously recorded on videotape facial actions scored from videotape in 2 s intervals for first 20 s of each phase raw scores of each facial action expressed	mean/95% confidence intervals for facial activity score / group / 13 phases reported in graph format data extracted from graphs	data extraction to obtain mean/SD facial score for circumcision phases circumcision (7 phases) = [application of forceps to foreskin excision] calculate arithmetic mean/group across phases of circumcision

Table 01 Trials assessing pain/behavior scores (*Continued*)

Study ID	scale	measurement method	data reported	data preparation
	stretching of mouth, horizontal stretching of mouth, lip pursing, taut tongue, chin quiver, tongue protrusion) higher score = more pain	as proportion of time observed/phase; poorly correlated facial actions deleted leaving 6 facial actions; the six scores were weighted and totaled to arrive at overal score for facial action		calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) SE = ((high CI - low CI)/2)/1.96 SD = SE (sqrt(n))
Taeusch 2002	infant behavior scale (1 - 7) adapted from other pain scores deep sleep - 1; REM sleep - 2; drowsy - 3 awake alert - 4; fussy - 5 mild to moderate cry - 6; continuous cry - 7 (Abu-Saad 1998)	behavior scored for every 3 min period during circumcision	mean pain scores / group / time period	data not included
Weatherstone 1993	newborn pain behavior scale adapted from 3 other scales (Brazelton 1973; Yarrow 1975; Ross 1988) score includes assessment of behavioral state, leg and arm movement, facial expression, torso movement, respiratory pattern, soothability, response to distress by caregivers, tactile stimulation	videotape of procedure scored in 30 s intervals	increase in mean/SD % of time behavior observed post-cirucmcision compared to pre- circumcision/ group	data not included

Table 02 Trials assessing heart rate outcome variables

Study ID	measurement method	data reported	preparation of data
Arnett 1990	HR measured by pulse oximetry at baseline, every min for 4 min, and 5 min post-circumcision	mean HR/group/phase reported in graph format	graph extraction for means graph extraction for SDs (averaged over 4 phases of the circumcision procedure) "procedure" = [min 1 to min 4]; steps not described or standardized
Benini 1993	HR measured continuously by	outcome data (mean/SDs)	calculate arithmetic mean/group

Table 02 Trials assessing heart rate outcome variables (*Continued*)

Study ID	measurement method	data reported	preparation of data
	pulse oximeter	obtained from authors	across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [application of dorsal clamp, incision, adhesion lysis, Gomco clamp on, foreskin excision, Gomco clamp off, restraints removed]
Butler-O'Hara 1998	HR monitored continuously using cardiac monitor	mean/SD heart rate (bpm) at completion of circumcision by group mean/SD heart rate (bpm) change from baseline at completion of circumcision by group	data entered into meta-analysis as reported
Joyce 2001	HR monitored continuously using cardiac monitor	data (bpm) obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [cut, end of procedure]
Hardwick-Smith 1998	HR monitored continuously using cardiac monitor highest HR recorded at start of each interval	increase in HR from baseline per group for operative interval reported in graph format	graphs did not depict SDs (whiskers); researchers reported control infants had signifcantly greater increase over baseline during 7 out 10 operative intervals; they did not comment on differences between the groups/interval
Herschel 1998	HR monitored continuously using cardiac monitor	mean/SD HR (bpm) change from baseline during procedure by group	data entered into meta-analysis as reported "procedure" = lateral clamp of foreskin to foreskin excision
Holliday 1999	HR monitored continuously using cardiac monitor HR recorded every 5 min before, during, 5 and 20 min after circumcision	mean/SD HR (bpm)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction to obtain mean/SD during procedure
Holve 1983	HR continuously recorded using monitor	mean change in HR from baseline (bpm) weighted averages/group for 6 phases reported in graphic format	no SDs, SEs depicted on graphs

Table 02 Trials assessing heart rate outcome variables (*Continued*)

Study ID	measurement method	data reported	preparation of data
Howard 1994	HR counted via auscultation every 30 s	mean/SD HR (bpm) / group / phase mean/SD HR (bpm) change from baseline by group/phase	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [dissection, clamp on, excision, clamp off]
Howard 1999	HR recorded every 60 s using cardiac monitor	- mean/SE HR (bpm) during procedure by group	means included as reported convert SE to SD using formula: SD = SE (sqrt (n)) "procedure" = [block administration to recovery; includes 4 min WT and Gomco clamp left on for 5 min]
Kass 2001	HR monitored at 1 min intervals during procedure	mean/SD HR (bpm) during procedure by group obtained from authors	mean/SD entered into meta-analysis
Kurtis 1999	HR monitored continuously using cardiac monitor	mean/SD % HR change from baseline during procedure by clamp used (Mogen, Gomco) and by penile block status (block, no block)	data entered into meta-analysis as reported "procedure" = [lysing adhesions to 60 sec after closing clamp]
Lander 1997	HR monitored continuously using cardiac monitor	mean/SD HR (bpm) change from baseline by phase by group	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [separation, clamp on, clamp off]
Macke 2001	HR recorded every 15 s using cardiac monitor	mean/SD HR (bpm) during circumcision by group	data included as reported
Marchette 1989	HR monitored	mean HR /phase / group no SDs reported	not included
Marchette 1991	HR monitored and data collected during 14 cirumcision steps	RMANOVA over 14 steps	not included
Masciello 1990	HR monitored continuously using cardiac monitor peak HR during each step recorded	mean HR as a percent of baseline HR reported in graphic format	not included
Maxwell 1987	HR monitored continuously by pulse oximeter peak HR during each period	mean/SD HR change / group / period as a % of control (baseline) reported in graph format	graph extraction to obtain mean/SD during circumcision procedure

Table 02 Trials assessing heart rate outcome variables (*Continued*)

Study ID	measurement method	data reported	preparation of data
	recorded		
Mohan 1998	HR monitored continuously by pulse oximeter HR recorded at each of 9 steps	mean HR / group / procedure step reported in graph format	graph extraction to obtain mean HR / group / procedure step substituted weighted average treatment-specific SDs from 5 studies: Benini 1993, Joyce 2001, Lander 1997, Taddio 1997, Woodman 1999 for EMLA and from 3 studies: Herschel 1998, Kass 2001, Zolnoski 1993 for sucrose
Mudge 1989	HR measured by monitor at 5 time points during circumcision	mean HR / group / event reported in graph format RMANOVA for 4 events (adhesion breakdown to clamp off)	graph extraction to obtain mean HR/group for events 2 - 5 calculate arithmetic mean HR / group across 4 phases of the procedure (adhesion breakdown, clamp on, tighten clamp, clamp off) substitute SDs from Woodman 1999 who applies same outcome to same comparison
Newton 1999	HR monitored continuouslly by pulse oximeter HR recorded at 10 s intervals	mean/SD HR / group at baseline, injection, clamp application	included as reported
Spencer 1992	HR monitored by pulse oximeter recorded highest HR for each of 6 events	mean change in HR (bpm) from baseline / group / event	no SDs, not included
Taddio 1997	HR continuously monitored by cardiac monitor	mean/SD HR (bpm) change from baseline during procedure	data included as reported "procedure" = [forcep application, lysis of adhesions, dorsal incision, clamp application, pull foreskin through clamp, tighten clamp, cut foreskin] procedure does not include clamp removal at 5 min after cut foreskin
Weatherstone 1993	HR monitored at 5 min intervals for 20 min	none	not included
Williamson 1983	HR monitored continuously	mean/SD HR (bpm) change from baseline for 3 min "dissection" period	mean/SD data included as reported dissection does not include clamp application
Woodman 1999	HR monitored continuously using pulse oximeter recorded peak heart rate during or immediately following 7 stages of circumcision procedure	mean/SD peak HR (bpm) / group	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations

Table 02 Trials assessing heart rate outcome variables *(Continued)*

Study ID	measurement method	data reported	preparation of data
			of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [clamp, adhesionlysis, dorsal clamp, bell on, clamp tightening, bell off]
Zolnoski 1993	HR monitored continuously using cardiac monitor HR (bpm) recorded at beginning of 7 procedure steps	- mean/SD HR (bpm) /group for 4 procedure steps	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y))

Table 03 Trials assessing cry outcome variables

Study ID	measurement method	data reported	data preparation
Benini 1993	cry tape recorded	% time crying/phase (duration of time crying) reported in graph format	means, SEs (assumed) extracted from graph; calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [dorsal clamp, incision, lysis, clamp on, foreskin cut, clamp off, unrestrained]
Blass 1991	cry tape recorded	mean % time crying (duration of time crying) during entire procedure reported in graph format	- graph extraction of group mean/SE; - SD calulated using formula: SD = SE (sqrt (n))
Holve 1983	cry tape recorded	mean % time crying /interval reported in graphic format	no SDs, not included
Hardwick-Smith 1998	cry tape recorded	mean/SD minutes crying/group during operative interval (lateral clamping to clamp removal)	convert reported time to seconds data included in meta-analysis
Howard 1994	used stopwatch to time crying during each phase	mean/SD % time crying by group/phase mean/SD % time crying change from baseline/group/phase	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [dissection, clamp on, excision, clamp off]

Table 03 Trials assessing cry outcome variables (*Continued*)

Study ID	measurement method	data reported	data preparation
Joyce 2001	behavior videotaped calculated total time crying from start of foreskin cut until crying ceased or 30 min elapsed	cry time (min) for each subject obtained from authors	calculate mean/SD time crying in min and sec/group
Kass 2001	primary outcome variable behavior videotaped	mean/SD time crying (s) /group during procedure obtained from authors	mean/SD included in meta-analysis
Kurtis 1999	behavior videotaped calculated time crying using stopwatch	mean/SD % time crying during procedure reported by clamp used (Mogen, Gomco) and by penile block status (block, no block)	mean/SD included as reported
Lander 1997	behavior videotaped proportion of time crying calculated/subject	mean/SD % time crying/interval	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y))- "procedure" = [separation, clamp on, clamp off)
Macke 2001	continuous vocalizations of 15 s or more classified as crying and tape recorded total s used to calculate % time crying	mean/SD % time crying during circumcision period by group	data included as reported
Mohan 1998	stopwatch used to measure duration of crying	mean % time crying / group during entire procedure	not included
Mudge 1989	crying time tape recorded during procedure measured by stop watch	mean total crying time (s)/group for entire procedure t-statistic, p value	mean crying time included as reported SD imputed from t statistic procedure includes 5 events (baseline, adhesion breakdown, clamp on, tighten clamp, clamp off)
Spencer 1992	cry duration measured by modified Brazelton Neonatal behavioral Scale (Stang et al, 1988) 6 behavioral states recorded for each of 6 events	mean % change from baseline / group	no SDs, not included
Stang 1988	not described	mean/SEM % time crying during circumcision period/group	means included as reported SEM converted to SD using formula: SD = SEM (sqrt (n))
Taddio 1997	behavior videotaped calculated % of time crying during each phase	mean/SD % increase from baseline in time crying during procedure	data included as reported "procedure" = [forcep application, lysis of adhesions, dorsal incision, clamp application, pull foreskin

Table 03 Trials assessing cry outcome variables (*Continued*)

Study ID	measurement method	data reported	data preparation
			through clamp, tighten clamp, cut foreskin] does not include clamp removal at 5 min after foreskin cut
Williamson 1983	time crying recorded using event marker	mean/SD % time crying change from baseline during 3 min dissection period	mean/SD data included as reported
Woodman 1999	behavior videotaped recorded time crying based on facial actions with or without audible cry	mean/SD time crying (s) for 6 phases by group	add time crying for 6 of 8 stages (clamp, adhesionlysis, dorsal clamp, clamp on, clamp tightening, clamp off) to obtain total time crying during procedure add SD to obtain total SD for group
Zahorodny 1998	not reported	mean % time crying/group	substituted weighted average treatment-specific SDs from three other studies: Benini 1993, Lander 1997, Taddio 1997 for EMLA vs placebo/ no treatment substituted treatment-specific SDs from Blass 1991 A (also versus water) for sucrose vs placebo/ no treatment substituted with the SDs used in the two above comparisons for EMLA vs sucrose
Zolnoski 1993	cry tape recorded, measured using stopwatch	time cry (s)/infant	mean/SD cry time (s)/group calculated

Table 04 Trials assessing oxygen saturation outcome variables

Study ID	measurement method	data reported	data preparation
Arnett 1990	measured by pulse oximetry at baseline, every min for 4 min during procedure, and 5 min postcircumcision	mean oxygen saturation (%) / group / phase and SDs presented graphically	graph extraction of means, graph extraction of SDs, averaged over 4 phases
Benini 1997	O2sat continuously monitored using pulse oximeter	outcome data (mean/SD) obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) procedure = [application of dorsal clamp, incision, adhesion lysis, Gomco clamp on, foreskin excision, Gomco clamp off, restraints removed]

Table 04 Trials assessing oxygen saturation outcome variables (*Continued*)

Study ID	measurement method	data reported	data preparation
Hardwick-Smith 1998	O2sat monitored continuously by pulse oximeter, lowest O2sat recorded at the start of each interval during some intervals of procedure, O2sat not recorded in up to 50% of infants	mean/SD of O2sat (%)/group for operative intervals	data included in meta-analysis as reported "operative interval" = [llateral clamp, blunt dissection, dorsal clamp, adhesion takedown, Gomco bell on, Gomco clamp applied, Gomco clamp removed]
Herschel 1998	O2sat continuously monitored via pulse oximetry substantial proportion of data lost due to excessive motion (31% control, 10% DPNB, 8% sucrose)	mean/SD O2sat (%) change from baseline during operative procedure by group	data included in meta-analysis as reported "operative procedure" = [lateral clamp of foreskin, adhesion lysis, dorsal clamp, dorsal cut, foreskin retraction, Gomco application, Gomco tightened, foreskin excision]
Holliday 1999	O2sat continuously monitored, recorded every 5 min before, during, 5min and 20 min after circumcision	mean/SD O2sat (%)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction for mean/SD during procedure
Joyce 2001	O2sat monitored continuously using pulse oximeter recorded O2sat (%) at each of 6 data collection points	raw data per subject per 6 phases obtained from authors	calculate mean/SD by group/phase calculate arithmetic mean/group across phases of the procedure calculate variance for arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) procedure = [cut, end]
Kass 2001	monitored O2sat at 1 min intervals during procedure	mean/SD O2sat during procedure by group data obtained from authors	mean/SD included in meta-analysis
Kurtis 1999	O2sat (%) monitored continuously and transferred to computer	- mean/SD % change from baseline during procedure reported by clamp used (Mogen, Gomco) and by penile block status (block, no block)	data included in meta-analysis as reported procedure = [lysing adhesions to 60 sec after closing clamp]
Marchette 1991	tcpO2 monitored and recorded during 14 circumcision steps	RMANOVA over 14 steps	not included
Masciello 1990	O2sat monitored continuously by pulse oximeter lowest level during each interval recorded	mean O2sat / group / interval reported in graphic format	not included
Maxwell 1987	O2sat monitored continuously using pulse oximeter peak value during period recorded	mean/SD O2sat /group / period reported in graph format	graph extraction to obtain mean/SD during circumcision period

Mohan 1998	O2sat monitored continuously using pulse oximeter recorded at each of 9 procedure steps	mean O2sat / group / procedure step reported in graph format	graph extraction to obtain mean O2sat / group / step substituted weighted average treatment-specific SDs from 3 trials: Benini 1993, Joyce 2001, Woodman 1999 for EMLA and from 2 trials: Herschel 1998, Kass 2001 for sucrose
Mudge 1989	O2sat measured by pulse oximeter and recorded at five time points during circumcision	mean O2sat(%) /group/event reported in graph format	graph extraction to obtain mean O2sat/group for events 2 - 5 calculate arithmetic mean O2sat / group across 4 phases of the procedure (adhesion breakdown, clamp on, tighten clamp, clamp off)
Spencer 1992	O2sat monitored by pulse oximeter recorded lowest level for each of 6 events	mean O2sat % change from baseline / group / event	no SDs, not included
Weatherstone 1993	O2sat monitored at 5 min intervals for 20 min	none	not included
Williamson 1983	O2sat measured using transcutaneous electrode (tcpO2)	mean/SD O2sat (torr) change from baseline for 3 min dissection period	data included in meta-analysis as reported dissection does not include clamp application
Woodman 1999	O2sat monitored continuously using pulse oximeter recorded peak/nadir during or immediately following 7 stages of circumcision procedure	- mean/SD peak/nadir O2sat / stage / group	calculate arithmetic mean/group across phases of the procedure calculate variance for arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) procedure = [clamp, adhesiolysis, dorsal clamp, clamp on, clamp tightening, clamp off)

Table 05 Trials assessing respiratory rate outcome variables

Study ID	measurement method	data reported	preparation of data
Butler-OHara 1998	RR monitored continuously starting after anesthetic administration, and 1 and 4 hr after procedure	RR variable and difficult to evaluate not reported	not included in meta-analysis
Hardwick-Smith 1998	highest RR recorded at start of each interval (anesthesia/ restraint, 3 min post restraint/ anesthesia, lateral clamp, blunt dissection, dorsal clamp, adhesion breakdown, Gomco bell on, Gomco clamp on, Gomco clamp	mean/SD increase from baseline RR/group for operative intervals (lateral clamping to Gomco clamp removal)	data included in meta-analysis as reported

Table 05 Trials assessing respiratory rate outcome variables *(Continued)*

Study ID	measurement method	data reported	preparation of data
	removed)		
Holliday 1999	RR monitored continuously using cardiac monitor HR recorded every 5 min before, during, 5 and 20 min after circumcision	mean/SD RR (bpm)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction for mean/SD during procedure
Howard 1994	RR assessed by visual observation every 30 s	mean/SD RR (rpm) / group / phase mean/SD RR (rpm) change from baseline by group/phase	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [dissection, clamp on, excision, clamp off]
Howard 1999	RR counted and recorded every 60 s	mean/SE RR (rpm) by group for procedure	means included as reported convert SE to SD using formula: SD = SE (sqrt (n)) "procedure" = [block administration to recovery; includes 4 min WT and Gomco clamp left on for 5 min]
Joyce 2001	RR monitored continuously, recorded at 6 data collection points	raw data obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [cut, end of procedure]
Kurtis 1999	RR monitored continuously using physiologic monitor	mean/SD % change from baseline during procedure reported by clamp used (Mogen, Gomco) and by penile block status (block, no block)	data entered into meta-analysis as reported "procedure" = [lysing adhesions to 60 sec after closing clamp]
Mudge 1989	RR measured by pneumography monitor at 5 time points	mean RR / group / event reported in graph format RMANOVA for 4 events (adhesion breakdown to clamp off)	graph extraction to obtain mean RR/group for events 2 - 5 calculate arithmetic mean RR / group across 4 phases of the procedure (adhesion breakdown, clamp on, tighten clamp, clamp off)
Weatherstone 1993	RR monitored at 5 min intervals for 20 min	none	not included

Table 06 Trials assessing biochemical outcome variables

Study ID	measurement method	data reported	data preparation
Masciello 1990	blood drawn via heel stick 30 minutes post-circumcision	mean/SD plasma cortisol levels in mg/dL	mg/dL multiplied by 27.59 = nmol/L nmol/L included in meta-analysis
Stang 1988	blood drawn via heel stick for 1/2 subjects at 30 min post-circumcision, and 90 min for remaining 1/2 subjects	mean/SEM plasma cortisol levels in nmol/L and ug/dL	means (nmol/L) included in meta-analysis SEM converted to SD using formula: SD = SEM (sqrt(n))
Williamson 1986	blood drawn by heel stick at baseline and 30 min post-circumcision	mean/SEM plasma cortisol levels in ug/dL	SEM converted to SD using formula: SD = SEM (sqrt(n)) ug/dL
Holliday 1999	serum B-endorphin levels - blood sample taken before and 20 min post-circumcision	mean/SD / group in pmol/L	data included as reported
Joyce 2001	salivary cortisol samples collected at baseline abd 30 min after procedure	mean/SD before/after no units of measurement results not broken down by group	not included
Kurtis 1999	salivary cortisol	collected sample at baseline and 30 min post-circumcision	mean/SD included as reported
Stang 1997	plasma cortisol 30 min after beginning of circumcision	mean/SD / group nmol/dL and ug/dL	mean /SD (nmol/dL) included as reported
Weatherstone 1993	serum B-endorphin level taken pre-operatively and 15 min after circumcision	mean/SD B-endorphin level (pg/mL) for pre and post circumcision period/group	mean/SD level for post-circumcision period included as reported
Williamson 1986	plasma cortisol obtained at baseline and 30 min after Gomco clamp applied	mean/SEM plasma cortisol levels (ug/dL)/group	ug/dL multiplied by 27.59 = nmol/L SEM converted to SD using formula: SD = SEM (sqrt(n))

Table 07 Trials assessing blood pressure outcome variables

Study ID	measurement method	data reported	data preparation
Holliday 1999	systolic BP monitored continuously using cardiac monitor HR recorded every 5 min before, during, 5 and 20 min after circumcision	mean/SD BP (mmHg)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction for mean/SD during procedure
Marchette 1991	systolic and diastolic BP monitored and recorded during 14 steps of the cirumcision procedure	RMANOVA over 14 steps	not included
Maxwell 1987	BP measured by Doppler every 5 min	mean/SD systolic BP change as a % of control / group / period reported in graph format	graph extraction to obtain mean/SD during circumcision period

Table 07 Trials assessing blood pressure outcome variables ***(Continued)***

Study ID	measurement method	data reported	data preparation
Mohan 1998	systolic and diastolic BP measured over upper arm at each of 9 procedural steps	mean systolic and diastolic BP (mm Hg) reported in graph format	graph extraction to obtain mean / group / step substituted treatment-specific SDs from Taddio 1997 for EMLA; no SDs available for sucrose
Taddio 1997	systolic and diastolic BP measured at baseline and during lysis of adhesions	mean/SD increase mm Hg in systolic and diastolic BP	data included as reported
Weatherstone 1993	BP monitored at 5 min intervals for 20 min	none	not included

Table 08 Trials reporting adverse effects

Study ID	intervention(s)	adverse effects
Arnett 1990	0.4 ml lidocaine DPNB (n=23) 0.4 ml saline DPNB (n=22) control (n=7)	lidocaine group - 1 emesis treated with suction saline group - 2 bleeding post-procedure, 1 required suture control - 1 bleeding post-procedure controlled with pressure
Butler-O'Hara 1998	0.5 ml LP cream (n=21) 0.7 ml - 1.0 ml lidocaine DPNB + placebo cream (n=23)	DPNB group - 10 hematoma; 1 penile edema on day 5 LP cream group - 3 erythema
Holve 1983 & (primary study) Dixon 1984	0.8 ml lidocaine DPNB (n=15) 0.8 ml saline DPNB (n=8) control (n=8)	lidocaine group - 1 small unilateral hematoma
Holliday 1999	0.8 ml lidocaine DPNB + placebo cream (n=19) placebo cream (n=19) original protocol included LP cream group (n=12)	LP cream group - 2 redness and blistering of foreskin, LP cream group discontinued
Lander 1997	2 g LP cream (n=15) placebo cream (n=12) 0.8 ml lidocaine DPNB (n=14) 0.8 ml lidocaine RB (n=13)	placebo group - 1 apnea and emesis, 1 choking and apnea
Newton 1999	0.8 ml lidocaine DPNB (n=92) 0.8 ml buffered lidocaine DPNB (n=102)	lidocaine group - 4 had minor bleeding buffered lidocaine group - 6 had minor bleeding
Stang 1988	0.8 ml lidocaine DPNB (n=20) 0.8 ml saline DPNB (n=20) control (n=20)	occasional insignificant bleeding - groups and numbers not specified
Taddio 1997	1 g LP cream (n=29) 1 g placebo cream (n=30)	LP cream group - 12 minor foreskin pallor, 1 mild edema placebo group - 4 minor foreskin pallor
Williamson 1997	lidocaine DPNB (n=20) control (n=10)	DPNB group - 9 bleeding, 12 swelling, 1 erythema control group - 5 bleeding, 5 swelling, 1 hematoma, 3 erythema
Zolnoski 1993	2.4 ml 24% sucrose (n=10) 2.4 ml water (n=10)	sucrose group - 1 gagging water group - 2 regurgitation after circumcision

GRAPHS

Comparison 01 DPNB versus no treatment or sham

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Cry time (by unit)	6	212	Standardised Mean Difference (Fixed) 95% CI	-1.74 [-2.06, -1.41]
03 Heart rate (by unit)	8	352	Standardised Mean Difference (Fixed) 95% CI	-1.63 [-1.88, -1.38]
04 Heart rate (by wait time)			Standardised Mean Difference (Fixed) 95% CI	Subtotals only
05 Heart rate (by clamp)			Standardised Mean Difference (Fixed) 95% CI	Subtotals only
06 Oxygen saturation (by unit)	6	296	Weighted Mean Difference (Fixed) 95% CI	3.21 [2.69, 3.72]
07 Transcutaneous oxygen saturation - change from baseline	1	30	Weighted Mean Difference (Fixed) 95% CI	9.30 [1.75, 16.85]
08 Respiratory rate (by unit)	3	86	Standardised Mean Difference (Fixed) 95% CI	-0.07 [-0.50, 0.36]
09 Systolic blood pressure (by unit)	2	68	Standardised Mean Difference (Fixed) 95% CI	-0.66 [-1.18, -0.13]
10 Serum cortisol (nmol/dL) 30 min post	4	102	Weighted Mean Difference (Fixed) 95% CI	-70.11 [-142.13, 1.91]
11 Salivary cortisol increase (ug/dL) from baseline to 30 min post	1	48	Weighted Mean Difference (Fixed) 95% CI	-0.54 [-1.08, 0.00]
12 B-endorphin (pmol/L)	1	38	Weighted Mean Difference (Fixed) 95% CI	21.00 [-73.45, 115.45]

Comparison 02 Ring block versus no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cry time (by unit)	2	65	Standardised Mean Difference (Fixed) 95% CI	-1.27 [-1.82, -0.72]
02 Heart rate (bpm) change-from-baseline	1	25	Weighted Mean Difference (Fixed) 95% CI	-29.27 [-51.96, -6.58]
03 Oxygen saturation (%) change-from-baseline	1	40	Weighted Mean Difference (Fixed) 95% CI	3.84 [-0.94, 8.62]
04 Respiratory rate (rpm) change-from-baseline	1	40	Weighted Mean Difference (Fixed) 95% CI	-5.69 [-16.02, 4.64]

Comparison 03 EMLA versus placebo or no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score	2	86	Standardised Mean Difference (Fixed) 95% CI	-0.59 [-1.02, -0.16]
02 Cry time (by unit)	6	190	Standardised Mean Difference (Fixed) 95% CI	-0.78 [-1.08, -0.49]
03 Heart rate (by unit)	5	144	Weighted Mean Difference (Fixed) 95% CI	-14.62 [-19.36, -9.87]
04 Oxygen saturation (%)	3	78	Weighted Mean Difference (Fixed) 95% CI	0.90 [-0.19, 2.00]
05 Respiratory rate (rpm)	1	10	Weighted Mean Difference (Fixed) 95% CI	-4.31 [-20.79, 12.17]
06 Systolic blood pressure (mmHg) change-from-baseline	1	38	Weighted Mean Difference (Fixed) 95% CI	-3.00 [-15.50, 9.50]

07 Diastolic blood pressure (mmHg) change-from-baseline	1	38	Weighted Mean Difference (Fixed) 95% CI	-5.00 [-23.60, 13.60]

Comparison 04 Topical lidocaine versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Cry time (s)	2	85	Weighted Mean Difference (Fixed) 95% CI	-59.75 [-99.14, -20.36]
03 Heart rate (bpm)	2	85	Weighted Mean Difference (Fixed) 95% CI	-9.20 [-14.32, -4.07]
04 Oxygen saturation (%)	2	85	Weighted Mean Difference (Fixed) 95% CI	-0.50 [-1.75, 0.75]
05 Respiratory rate (rpm)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
06 B-endorphin (pg/mL)	1	30	Weighted Mean Difference (Fixed) 95% CI	-49.00 [-88.74, -9.26]

Comparison 05 Sucrose versus water or no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Cry time (by unit)	5	123	Standardised Mean Difference (Fixed) 95% CI	0.07 [-0.31, 0.44]
03 Heart rate (by unit)	3	146	Weighted Mean Difference (Fixed) 95% CI	-3.46 [-8.98, 2.07]
04 Oxygen saturation (by unit)	2	126	Weighted Mean Difference (Fixed) 95% CI	1.82 [0.51, 3.13]
05 Serum cortisol (nmol/dL) 30 min post	1	40	Weighted Mean Difference (Fixed) 95% CI	68.90 [-53.94, 191.74]

Comparison 06 Acetaminophen versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain / behavior score			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Cry time (%)	2	104	Weighted Mean Difference (Fixed) 95% CI	-1.76 [-8.26, 4.74]
03 Heart rate (bpm)	2	104	Weighted Mean Difference (Fixed) 95% CI	2.27 [-2.89, 7.44]
04 Respiratory rate (rpm)	1	44	Weighted Mean Difference (Fixed) 95% CI	-3.73 [-11.00, 3.54]

Comparison 07 DPNB versus EMLA

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Cry time (%)	1	29	Weighted Mean Difference (Fixed) 95% CI	-10.00 [-29.74, 9.74]
03 Heart rate (by unit)	3	133	Weighted Mean Difference (Fixed) 95% CI	-16.85 [-22.69, -11.00]
04 Heart rate by wait time			Standardised Mean Difference (Fixed) 95% CI	Subtotals only
05 Respiratory rate (rpm)	1	60	Weighted Mean Difference (Fixed) 95% CI	-2.90 [-7.47, 1.67]

Comparison 08 DPNB versus sucrose

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score	1	47	Weighted Mean Difference (Fixed) 95% CI	-3.23 [-4.65, -1.81]
02 Cry time (s)	1	47	Weighted Mean Difference (Fixed) 95% CI	-166.00 [-210.54, -121.46]
03 Heart rate (by unit)	2	126	Weighted Mean Difference (Fixed) 95% CI	-26.56 [-33.36, -19.76]
04 Oxygen saturation (by unit)	2	126	Weighted Mean Difference (Fixed) 95% CI	0.25 [-0.78, 1.27]

Comparison 09 DPNB versus ring block

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cry time (%)	1	27	Weighted Mean Difference (Fixed) 95% CI	6.33 [-15.50, 28.16]
02 Heart rate (bpm) change-from-baseline	1	27	Weighted Mean Difference (Fixed) 95% CI	4.43 [-14.07, 22.93]

Comparison 10 DPNB versus local block

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Serum cortisol (nmol/dL) 30 min post	1	18	Weighted Mean Difference (Fixed) 95% CI	306.27 [141.33, 471.21]

Comparison 11 Ring block versus EMLA

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Heart rate (bpm) change-from-baseline	1	28	Weighted Mean Difference (Fixed) 95% CI	-3.17 [-20.46, 14.12]
02 Cry time (%)	1	28	Weighted Mean Difference (Fixed) 95% CI	-16.33 [-35.66, 3.00]

Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Cry time (%)	1	194	Weighted Mean Difference (Fixed) 95% CI	9.00 [-11.71, 29.71]
03 Heart rate (bpm)	1	194	Weighted Mean Difference (Fixed) 95% CI	-4.20 [-10.51, 2.11]
04 Oxygen saturation (%)	1	194	Weighted Mean Difference (Fixed) 95% CI	0.50 [-0.87, 1.87]
05 Serum cortisol (nmol/dL) 30 min post	1	40	Weighted Mean Difference (Fixed) 95% CI	35.80 [-105.62, 177.22]

Comparison 13 EMLA versus 30% topical lidocaine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cry time (s)	1	40	Weighted Mean Difference (Fixed) 95% CI	-17.00 [-75.00, 41.00]

02 Heart rate (bpm)	1	40	Weighted Mean Difference (Fixed) 95% CI	-11.88 [-19.40, -4.36]
03 Oxygen saturation (%)	1	40	Weighted Mean Difference (Fixed) 95% CI	-0.17 [-1.44, 1.10]

Comparison 14 EMLA versus sucrose

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cry time (%)	1	26	Weighted Mean Difference (Fixed) 95% CI	-10.00 [-26.74, 6.74]
02 Heart rate (bpm)	1	41	Weighted Mean Difference (Fixed) 95% CI	-9.35 [-20.08, 1.38]
03 Oxygen saturation (%)	1	41	Weighted Mean Difference (Fixed) 95% CI	-0.82 [-2.63, 0.99]
04 Systolic blood pressure (mmHg)	1	41	Weighted Mean Difference (Fixed) 95% CI	Not estimable
05 Diastolic blood pressure (mmHg)	1	41	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 15 EMLA versus music

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cry time (min)	1	12	Weighted Mean Difference (Fixed) 95% CI	0.38 [-3.68, 4.44]
02 Heart rate (bpm)	1	12	Weighted Mean Difference (Fixed) 95% CI	2.31 [-15.99, 20.61]
03 Oxygen saturation (%)	1	12	Weighted Mean Difference (Fixed) 95% CI	0.19 [-3.56, 3.94]
04 Respiratory rate (rpm)	1	12	Weighted Mean Difference (Fixed) 95% CI	1.52 [-13.60, 16.64]

Comparison 16 Music versus no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cry time (min)	1	12	Weighted Mean Difference (Fixed) 95% CI	-1.58 [-5.81, 2.65]
02 Heart rate (bpm)	1	12	Weighted Mean Difference (Fixed) 95% CI	-7.89 [-41.37, 25.59]
03 Oxygen saturation (%)	1	12	Weighted Mean Difference (Fixed) 95% CI	2.51 [-0.62, 5.64]
04 Respiratory rate (rpm)	1	12	Weighted Mean Difference (Fixed) 95% CI	-5.83 [-21.41, 9.75]

COVER SHEET

Title	Pain relief for neonatal circumcision
Authors	Brady-Fryer B, Wiebe N, Lander JA
Contribution of author(s)	Brady-Fryer - protocol development; study selection; data extraction; contact authors; data preparation & analysis; write report Wiebe - data extraction; data preparation & analysis; write report Lander - protocol development and review; review draft and final report Brankston - study selection; data extraction
Issue protocol first published	2003/2
Review first published	2004/4
Date of most recent amendment	25 August 2004
Date of most recent SUBSTANTIVE amendment	01 May 2004

What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Fig. 1. Comparison 01 DPNB versus no treatment or sham

01.01 Pain score

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 01 Pain score

Study	DPNB		No treatment or sham		Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	(%)	95% CI
01 infant irritability score						
Arnett 1990	23	2.40 (1.20)	29	4.20 (0.90)	100.0	-1.80 [-2.39, -1.21]
Subtotal (95% CI)	23		29		100.0	-1.80 [-2.39, -1.21]
Test for heterogeneity: not applicable						
Test for overall effect z=5.98 p<0.00001						
02 modified behavioral pain scale (MBPS)						
Kass 2001	24	4.40 (2.80)	24	7.63 (1.71)	100.0	-3.23 [-4.54, -1.92]
Subtotal (95% CI)	24		24		100.0	-3.23 [-4.54, -1.92]
Test for heterogeneity: not applicable						
Test for overall effect z=4.82 p<0.00001						
03 author-created behavioural score						
Holliday 1999	19	14.10 (4.10)	19	22.90 (3.00)	100.0	-8.80 [-11.08, -6.52]
Subtotal (95% CI)	19		19		100.0	-8.80 [-11.08, -6.52]
Test for heterogeneity: not applicable						
Test for overall effect z=7.55 p<0.00001						
04 crying component of behavioural score						
Holliday 1999	19	6.90 (6.10)	19	16.70 (3.60)	100.0	-9.80 [-12.98, -6.62]
Subtotal (95% CI)	19		19		100.0	-9.80 [-12.98, -6.62]
Test for heterogeneity: not applicable						
Test for overall effect z=6.03 p<0.00001						

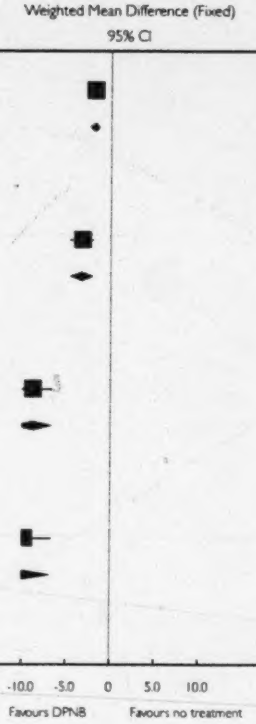


Fig. 2. Comparison 01 DPNB versus no treatment or sham

01.02 Cry time (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 02 Cry time (by unit)

Study	DPNB		No treatment or sham		Standardised Mean Difference (Fixed)	Weight	Standardised Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 in %							
Kurtis 1999 A	24	34.80 (38.50)	24	91.00 (16.80)		22.9	-1.86 [-2.55, -1.17]
Lander 1997	14	47.33 (29.97)	12	88.00 (14.32)		13.0	-1.63 [-2.54, -0.73]
Stang 1988 A	10	23.00 (33.98)	20	71.10 (31.75)		14.8	-1.44 [-2.29, -0.59]
Stang 1988 B	10	23.00 (33.98)	20	68.00 (34.88)		15.5	-1.27 [-2.10, -0.43]
Williamson 1983	20	16.70 (40.30)	10	93.10 (15.30)		11.7	-2.17 [-3.13, -1.21]
Subtotal (95% CI)	78		86			78.0	-1.67 [-2.04, -1.30]
Test for heterogeneity chi-square=2.51 df=4 p=0.64 I² =0.0%							
Test for overall effect z=8.80 p<0.00001							
02 in seconds							
Kass 2001	24	90.00 (87.00)	24	225.00 (39.00)		22.0	-1.97 [-2.67, -1.27]
Subtotal (95% CI)	24		24			22.0	-1.97 [-2.67, -1.27]
Test for heterogeneity: not applicable							
Test for overall effect z=5.52 p<0.00001							
Total (95% CI)	102		110			100.0	-1.74 [-2.06, -1.41]
Test for heterogeneity chi-square=3.06 df=5 p=0.69 I² =0.0%							
Test for overall effect z=10.36 p<0.00001							

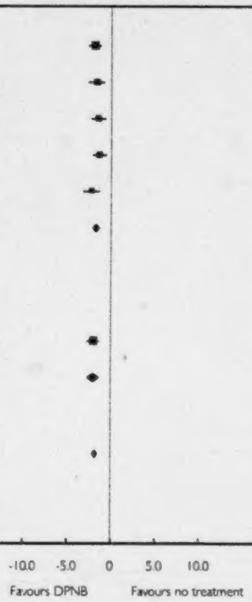


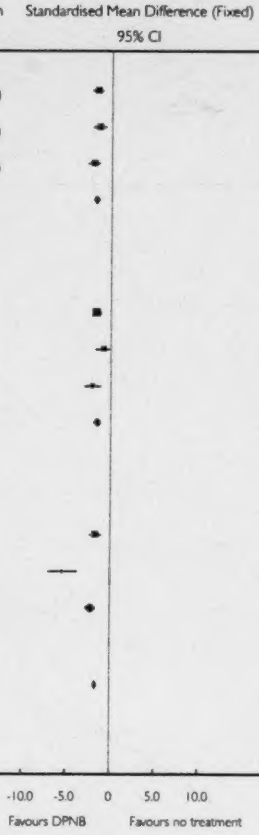
Fig. 3. Comparison 01 DPNB versus no treatment or sham

01.03 Heart rate (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 03 Heart rate (by unit)



Study	DPNB N	DPNB Mean(SD)	No treatment or sham N	No treatment or sham Mean(SD)	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 in bpm						
Arnett 1990	23	131.45 (19.41)	29	156.75 (12.98)	15.9	-1.55 [-2.17, -0.92]
Holliday 1999	19	159.46 (15.37)	19	180.77 (16.77)	12.6	-1.30 [-2.00, -0.59]
Kass 2001	24	133.03 (22.19)	24	178.76 (23.14)	12.8	-1.98 [-2.69, -1.28]
Subtotal (95% CI)	66		72		41.4	-1.61 [-2.00, -1.22]
Test for heterogeneity chi-square=1.89 df=2 p=0.39 I² =0.0%						
Test for overall effect z=8.06 p<0.00001						
02 in bpm change-from-baseline						
Herschel 1998	40	9.70 (17.30)	40	36.80 (17.10)	24.8	-1.56 [-2.06, -1.06]
Lander 1997	14	21.86 (26.04)	12	46.70 (33.47)	9.7	-0.81 [-1.62, 0.00]
Williamson 1983	20	3.40 (26.90)	10	54.10 (17.80)	7.2	-2.03 [-2.96, -1.09]
Subtotal (95% CI)	74		62		41.7	-1.47 [-1.86, -1.08]
Test for heterogeneity chi-square=4.04 df=2 p=0.13 I² =50.5%						
Test for overall effect z=7.39 p<0.00001						
03 in % change-from-baseline						
Kurtis 1999 A	24	13.30 (12.30)	24	32.10 (10.90)	14.6	-1.59 [-2.25, -0.94]
Maxwell 1987	20	3.10 (4.05)	10	33.30 (7.75)	2.4	-5.33 [-6.96, -3.69]
Subtotal (95% CI)	44		34		17.0	-2.11 [-2.72, -1.50]
Test for heterogeneity chi-square=17.30 df=1 p=<0.0001 I² =94.2%						
Test for overall effect z=6.79 p<0.00001						
Total (95% CI)	184		168		100.0	-1.63 [-1.88, -1.38]
Test for heterogeneity chi-square=26.31 df=7 p=0.0004 I² =73.4%						
Test for overall effect z=12.76 p<0.00001						

Fig. 4. Comparison 01 DPNB versus no treatment or sham

01.04 Heart rate (by wait time)

Review: Pain relief for neonatal circumcision
Comparison: 01 DPNB versus no treatment or sham
Outcome: 04 Heart rate (by wait time)

Study	DPNB N	DPNB Mean(SD)	No treatment or sham N	No treatment or sham Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 wait time after anesthetic administration </= 5 min							
Herschel 1998	40	9.70 (17.30)	40	36.80 (17.10)		53.3	-1.56 [-2.06, -1.06]
Kurtis 1999 A	24	13.30 (12.30)	24	32.10 (10.90)		31.4	-1.59 [-2.25, -0.94]
Williamson 1983	20	3.40 (26.90)	10	54.10 (17.80)		15.4	-2.03 [-2.96, -1.09]
Subtotal (95% CI)	84		74			100.0	-1.64 [-2.01, -1.27]
Test for heterogeneity chi-square=0.77 df=2 p=0.68 I² =0.0%							
Test for overall effect z=8.76 p<0.00001							
02 wait time after anesthetic administration > 5 min							
Holliday 1999	19	159.46 (15.37)	19	180.77 (16.77)		51.8	-1.30 [-2.00, -0.59]
Lander 1997	14	21.86 (26.04)	12	46.70 (33.47)		39.7	-0.81 [-1.62, 0.00]
Maxwell 1987	20	3.10 (4.05)	10	33.30 (6.75)		8.5	-5.79 [-7.53, -4.04]
Subtotal (95% CI)	53		41			100.0	-1.49 [-1.99, -0.98]
Test for heterogeneity chi-square=26.31 df=2 p=<0.0001 I² =92.4%							
Test for overall effect z=5.72 p<0.00001							
03 wait time after anesthetic administration - other wait time reported							
Kass 2001	24	133.03 (22.19)	24	178.76 (23.14)		100.0	-1.98 [-2.69, -1.28]
Subtotal (95% CI)	24		24			100.0	-1.98 [-2.69, -1.28]
Test for heterogeneity: not applicable							
Test for overall effect z=5.55 p<0.00001							

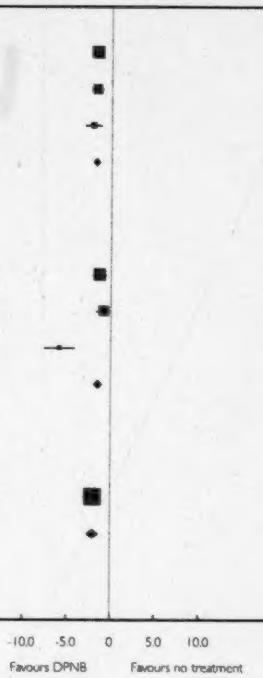


Fig. 5. Comparison 01 DPNB versus no treatment or sham

01.05 Heart rate (by clamp)

Review: Pain relief for neonatal circumcision
Comparison: 01 DPNB versus no treatment or sham
Outcome: 05 Heart rate (by clamp)

Study	DPNB N	DPNB Mean(SD)	No treatment or sham N	No treatment or sham Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 Gomco							
Arnett 1990	22	131.45 (19.41)	26	156.75 (12.98)		16.5	-1.53 [-2.18, -0.88]
Herschel 1998	40	9.70 (17.30)	40	36.80 (17.10)		27.7	-1.56 [-2.06, -1.06]
Holliday 1999	19	159.46 (15.37)	19	180.77 (16.77)		14.1	-1.30 [-2.00, -0.59]
Kass 2001	24	133.03 (22.19)	24	178.76 (23.14)		14.3	-1.98 [-2.69, -1.28]
Kurtis 1999 B	8	23.70 (13.90)	8	37.90 (12.60)		6.3	-1.01 [-2.07, 0.05]
Lander 1997	14	21.86 (26.04)	12	46.70 (33.47)		10.8	-0.81 [-1.62, 0.00]
Maxwell 1987	20	3.10 (4.05)	10	33.30 (6.75)		2.3	-5.79 [-7.53, -4.04]
Williamson 1983	20	3.40 (26.90)	10	54.10 (17.80)		8.0	-2.03 [-2.96, -1.09]
Subtotal (95% CI)	167		149			100.0	-1.60 [-1.86, -1.33]
Test for heterogeneity chi-square=29.70 df=7 p=0.0001 I² =76.4%							
Test for overall effect z=11.82 p<0.00001							
02 Mogen							
Kurtis 1999 A	16	8.00 (7.30)	16	29.10 (9.00)		100.0	-2.51 [-3.46, -1.56]
Subtotal (95% CI)	16		16			100.0	-2.51 [-3.46, -1.56]
Test for heterogeneity: not applicable							
Test for overall effect z=5.15 p<0.00001							

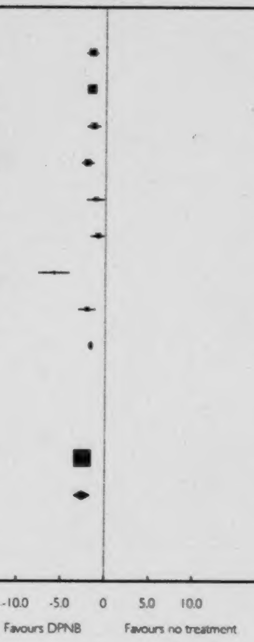


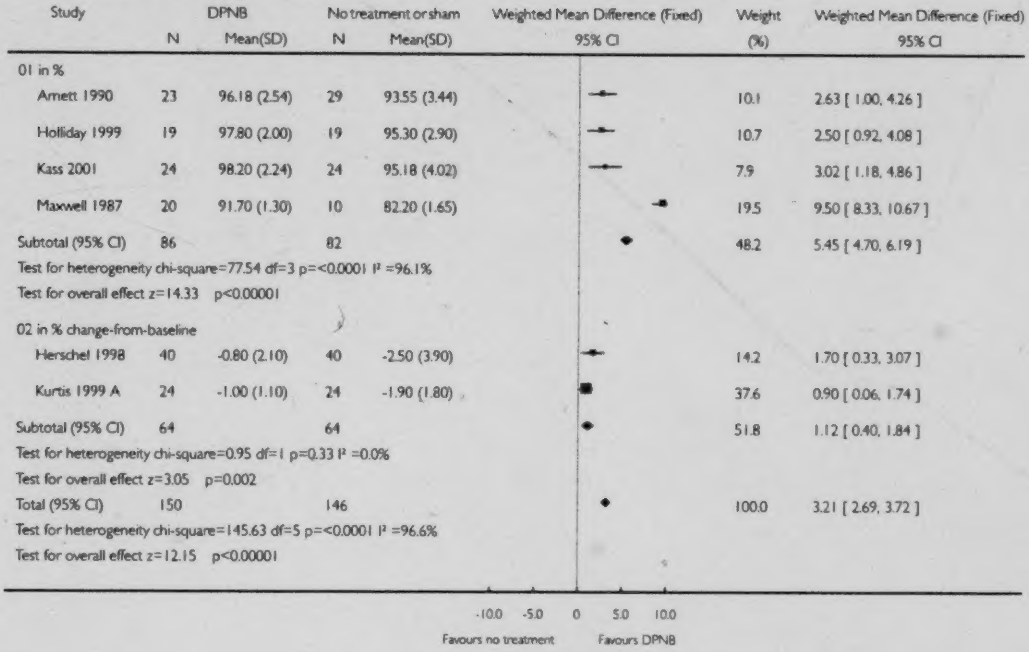
Fig. 6. Comparison 01 DPNB versus no treatment or sham

01.06 Oxygen saturation (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 06 Oxygen saturation (by unit)



Study	DPNB N	DPNB Mean(SD)	No treatment or sham N	No treatment or sham Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 in %						
Arnett 1990	23	96.18 (2.54)	29	93.55 (3.44)	10.1	2.63 [1.00, 4.26]
Holliday 1999	19	97.80 (2.00)	19	95.30 (2.90)	10.7	2.50 [0.92, 4.08]
Kass 2001	24	98.20 (2.24)	24	95.18 (4.02)	7.9	3.02 [1.18, 4.86]
Maxwell 1987	20	91.70 (1.30)	10	82.20 (1.65)	19.5	9.50 [8.33, 10.67]
Subtotal (95% CI)	86		82		48.2	5.45 [4.70, 6.19]
Test for heterogeneity chi-square=77.54 df=3 p=<0.0001 I² =96.1%						
Test for overall effect z=14.33 p<0.00001						
02 in % change-from-baseline						
Herschel 1998	40	-0.80 (2.10)	40	-2.50 (3.90)	14.2	1.70 [0.33, 3.07]
Kurtis 1999 A	24	-1.00 (1.10)	24	-1.90 (1.80)	37.6	0.90 [0.06, 1.74]
Subtotal (95% CI)	64		64		51.8	1.12 [0.40, 1.84]
Test for heterogeneity chi-square=0.95 df=1 p=0.33 I² =0.0%						
Test for overall effect z=3.05 p=0.002						
Total (95% CI)	150		146		100.0	3.21 [2.69, 3.72]
Test for heterogeneity chi-square=145.63 df=5 p=<0.0001 I² =96.6%						
Test for overall effect z=12.15 p<0.00001						

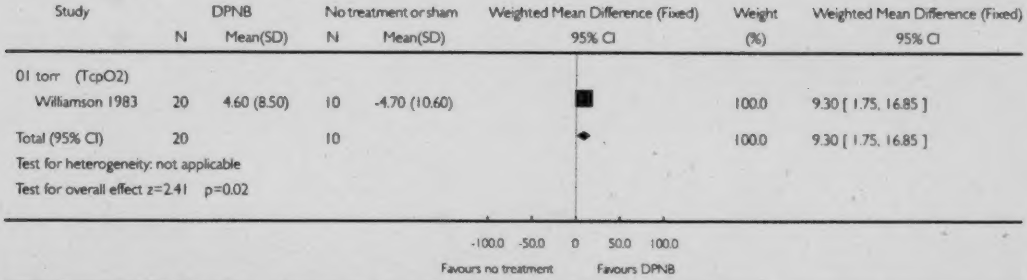
Fig. 7. Comparison 01 DPNB versus no treatment or sham

01.07 Transcutaneous oxygen saturation - change from baseline

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 07 Transcutaneous oxygen saturation - change from baseline

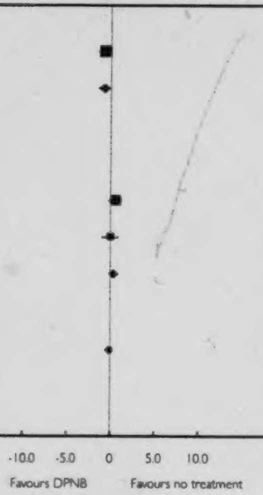


Study	DPNB N	DPNB Mean(SD)	No treatment or sham N	No treatment or sham Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 torr (TcpO2)						
Williamson 1983	20	4.60 (8.50)	10	-4.70 (10.60)	100.0	9.30 [1.75, 16.85]
Total (95% CI)	20		10		100.0	9.30 [1.75, 16.85]
Test for heterogeneity: not applicable						
Test for overall effect z=2.41 p=0.02						

Fig. 8. Comparison 01 DPNB versus no treatment or sham

01.08 Respiratory rate (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 01 DPNB versus no treatment or sham
Outcome: 08 Respiratory rate (by unit)



Study	DPNB N	DPNB Mean(SD)	No treatment or sham N	No treatment or sham Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 rpm							
Holliday 1999	19	53.60 (19.91)	19	64.43 (10.83)		43.5	-0.66 [-1.32, -0.01]
Subtotal (95% CI)	19		19			43.5	-0.66 [-1.32, -0.01]
Test for heterogeneity: not applicable							
Test for overall effect z=1.98 p=0.05							
02 in % change-from-baseline							
Kurtis 1999 A	16	0.40 (6.70)	16	-4.50 (9.50)		37.1	0.58 [-0.13, 1.29]
Kurtis 1999 B	8	5.10 (5.50)	8	5.00 (10.50)		19.4	0.01 [-0.97, 0.99]
Subtotal (95% CI)	24		24			56.5	0.39 [-0.19, 0.96]
Test for heterogeneity chi-square=0.85 df=1 p=0.36 I² =0.0%							
Test for overall effect z=1.31 p=0.2							
Total (95% CI)	43		43			100.0	-0.07 [-0.50, 0.36]
Test for heterogeneity chi-square=6.40 df=2 p=0.04 I² =68.7%							
Test for overall effect z=0.32 p=0.8							

Fig. 9. Comparison 01 DPNB versus no treatment or sham

01.09 Systolic blood pressure (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 09 Systolic blood pressure (by unit)

Study	DPNB		No treatment or sham		Standardised Mean Difference (Fixed)	Weight	Standardised Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 in mmHg							
Holliday 1999	19	89.59 (13.97)	19	89.95 (13.28)		68.5	-0.03 [-0.66, 0.61]
Subtotal (95% CI)	19		19			68.5	-0.03 [-0.66, 0.61]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							
02 in % change-from-baseline							
Maxwell 1987	20	5.40 (3.75)	10	15.00 (6.00)		31.5	-2.03 [-2.97, -1.09]
Subtotal (95% CI)	20		10			31.5	-2.03 [-2.97, -1.09]
Test for heterogeneity: not applicable							
Test for overall effect z=4.25 p=0.00002							
Total (95% CI)	39		29			100.0	-0.66 [-1.18, -0.13]
Test for heterogeneity chi-square=12.04 df=1 p=0.0005 I^2 =91.7%							
Test for overall effect z=2.45 p=0.01							

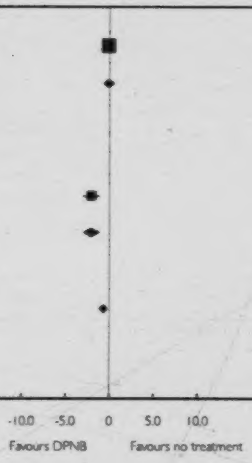


Fig. 10. Comparison 01 DPNB versus no treatment or sham

01.10 Serum cortisol (nmol/dL) 30 min post

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 10 Serum cortisol (nmol/dL) 30 min post

Study	DPNB		No treatment or sham		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Masciello 1990	9	549.04 (121.39)	9	532.48 (209.68)		20.7	16.56 [-141.73, 174.85]
Stang 1988 A	10	386.00 (160.99)	20	461.00 (125.21)		40.0	-75.00 [-188.87, 38.87]
Stang 1988 B	10	386.00 (160.99)	20	532.00 (196.77)		29.8	-146.00 [-277.88, -14.12]
Williamson 1986	11	631.81 (256.03)	13	631.81 (328.04)		9.5	0.00 [-233.86, 233.86]
Total (95% CI)	40		62			100.0	-70.11 [-142.12, 1.91]
Test for heterogeneity chi-square=2.78 df=3 p=0.43 I^2 =0.0%							
Test for overall effect z=1.91 p=0.06							

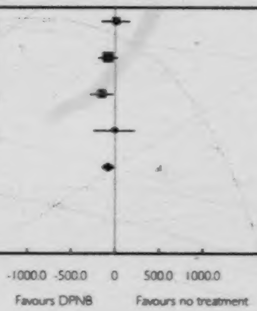


Fig. 11. Comparison 01 DPNB versus no treatment or sham

01.11 Salivary cortisol increase (ug/dL) from baseline to 30 min post

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 11 Salivary cortisol increase (ug/dL) from baseline to 30 min post

Study	DPNB		No treatment or sham		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Kurtis 1999 A	24	0.52 (0.98)	24	1.06 (0.92)		100.0	-0.54 [-1.08, 0.00]
Total (95% CI)	24		24			100.0	-0.54 [-1.08, 0.00]

Test for heterogeneity: not applicable

Test for overall effect z=1.97 p=0.05

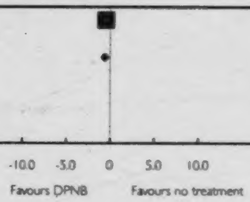


Fig. 12. Comparison 01 DPNB versus no treatment or sham

01.12 B-endorphin (pmol/L)

Review: Pain relief for neonatal circumcision

Comparison: 01 DPNB versus no treatment or sham

Outcome: 12 B-endorphin (pmol/L)

Study	DPNB		no treatment or sham		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Holliday 1999	19	326.00 (165.00)	19	305.00 (130.00)		100.0	21.00 [-73.45, 115.45]
Total (95% CI)	19		19			100.0	21.00 [-73.45, 115.45]

Test for heterogeneity: not applicable

Test for overall effect z=0.44 p=0.7

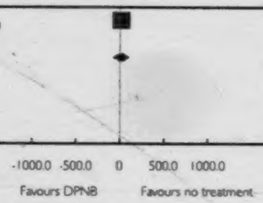


Fig. 13. Comparison 02 Ring block versus no treatment

02.01 Cry time (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 02 Ring block versus no treatment
Outcome: 01 Cry time (by unit)

Study	Ring block		No treatment		Standardised Mean Difference (Fixed)	Weight	Standardised Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 in %							
Lander 1997	13	41.00 (27.91)	12	88.00 (14.32)		30.4	-2.02 [-3.02, -1.03]
Subtotal (95% CI)	13		12			30.4	-2.02 [-3.02, -1.03]
Test for heterogeneity: not applicable							
Test for overall effect z=3.99 p=0.00007							
02 in seconds							
Hardwick Smith 1998	20	258.60 (115.80)	20	377.40 (130.80)		69.6	-0.94 [-1.60, -0.29]
Subtotal (95% CI)	20		20			69.6	-0.94 [-1.60, -0.29]
Test for heterogeneity: not applicable							
Test for overall effect z=2.81 p=0.005							
Total (95% CI)	33		32			100.0	-1.27 [-1.82, -0.72]
Test for heterogeneity chi-square=3.16 df=1 p=0.08 I² =68.4%							
Test for overall effect z=4.54 p<0.00001							

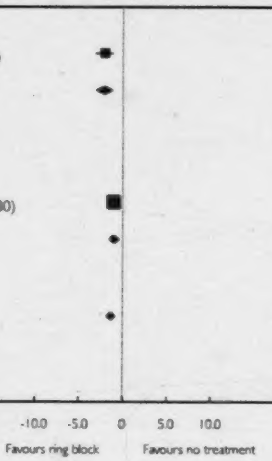


Fig. 14. Comparison 02 Ring block versus no treatment

02.02 Heart rate (bpm) change-from-baseline

Review: Pain relief for neonatal circumcision
Comparison: 02 Ring block versus no treatment
Outcome: 02 Heart rate (bpm) change-from-baseline

Study	Ring block		No treament		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Lander 1997	13	17.43 (22.99)	12	46.70 (33.47)		100.0	-29.27 [-51.96, -6.58]
Total (95% CI)	13		12			100.0	-29.27 [-51.96, -6.58]
Test for heterogeneity: not applicable							
Test for overall effect z=2.53 p=0.01							

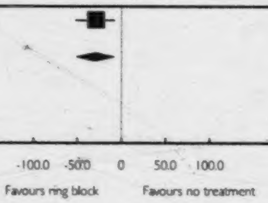


Fig. 15. Comparison 02 Ring block versus no treatment

02.03 Oxygen saturation (%) change-from-baseline

Review: Pain relief for neonatal circumcision

Comparison: 02 Ring block versus no treatment

Outcome: 03 Oxygen saturation (%) change-from-baseline

Study	Ring block		No treatment		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Hardwick Smith 1998	20	-5.02 (6.00)	20	-8.86 (9.10)		100.0	3.84 [-0.94, 8.62]
Total (95% CI)	20		20			100.0	3.84 [-0.94, 8.62]

Test for heterogeneity: not applicable

Test for overall effect z=1.58 p=0.1

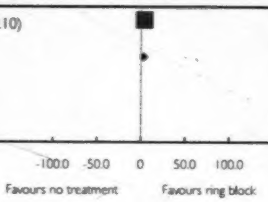


Fig. 16. Comparison 02 Ring block versus no treatment

02.04 Respiratory rate (rpm) change-from-baseline

Review: Pain relief for neonatal circumcision

Comparison: 02 Ring block versus no treatment

Outcome: 04 Respiratory rate (rpm) change-from-baseline

Study	Ring block		No treatment		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Hardwick Smith 1998	20	2.45 (18.39)	20	8.14 (14.74)		100.0	-5.69 [-16.02, 4.64]
Total (95% CI)	20		20			100.0	-5.69 [-16.02, 4.64]

Test for heterogeneity: not applicable

Test for overall effect z=1.08 p=0.3

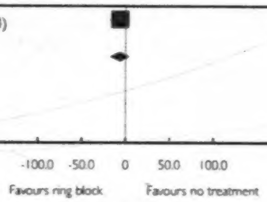


Fig. 17. Comparison 03 EMLA versus placebo or no treatment

03.01 Pain score

Review: Pain relief for neonatal circumcision
Comparison: 03 EMLA versus placebo or no treatment
Outcome: 01 Pain score

Study	EMLA N	EMLA Mean(SD)	Placebo N	Placebo Mean(SD)	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 neonatal facial coding system (NFCS)						
Benini 1993	14	356.75 (86.98)	13	423.86 (70.69)	30.1	-0.82 [-1.61, -0.03]
Subtotal (95% CI)	14		13		30.1	-0.82 [-1.61, -0.03]
Test for heterogeneity: not applicable						
Test for overall effect z=2.03 p=0.04						
02 NFCS - author-devised summary score						
Taddio 1997	29	0.86 (0.47)	30	1.06 (0.32)	69.9	-0.49 [-1.01, 0.03]
Subtotal (95% CI)	29		30		69.9	-0.49 [-1.01, 0.03]
Test for heterogeneity: not applicable						
Test for overall effect z=1.86 p=0.06						
Total (95% CI)	43		43		100.0	-0.59 [-1.02, -0.16]
Test for heterogeneity chi-square=0.45 df=1 p=0.50 I² =0.0%						
Test for overall effect z=2.67 p=0.008						

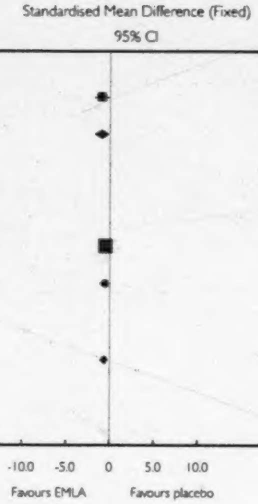


Fig. 18. Comparison 03 EMLA versus placebo or no treatment

03.02 Cry time (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 03 EMLA versus placebo or no treatment

Outcome: 02 Cry time (by unit)

Study	EMLA N	EMLA Mean(SD)	Placebo N	Placebo Mean(SD)	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 in %						
Benini 1993	14	77.07 (19.86)	13	88.33 (12.32)	14.7	-0.65 [-1.43, 0.12]
Lander 1997	15	57.33 (23.66)	12	88.00 (14.32)	11.8	-1.48 [-2.35, -0.61]
Zahorodny 1998	13	66.00 (24.50)	13	76.00 (20.57)	14.7	-0.43 [-1.21, 0.35]
Subtotal (95% CI)	42		38		41.2	-0.81 [-1.27, -0.34]
Test for heterogeneity chi-square=3.35 df=2 p=0.19 I² =40.3%						
Test for overall effect z=3.41 p=0.0007						
02 in minutes						
Joyce 2001	5	7.80 (2.77)	5	9.00 (3.08)	5.6	-0.37 [-1.63, 0.89]
Woodman 1999	20	2.58 (1.75)	21	3.70 (1.80)	22.6	-0.62 [-1.25, 0.01]
Subtotal (95% CI)	25		26		28.2	-0.57 [-1.13, -0.01]
Test for heterogeneity chi-square=0.12 df=1 p=0.73 I² =0.0%						
Test for overall effect z=1.98 p=0.05						
03 percent increase in time crying						
Taddio 1997	29	21.00 (27.00)	30	46.00 (25.00)	30.6	-0.95 [-1.49, -0.41]
Subtotal (95% CI)	29		30		30.6	-0.95 [-1.49, -0.41]
Test for heterogeneity: not applicable						
Test for overall effect z=3.44 p=0.0006						
Total (95% CI)	96		94		100.0	-0.78 [-1.08, -0.49]
Test for heterogeneity chi-square=4.40 df=5 p=0.49 I² =0.0%						
Test for overall effect z=5.15 p<0.00001						

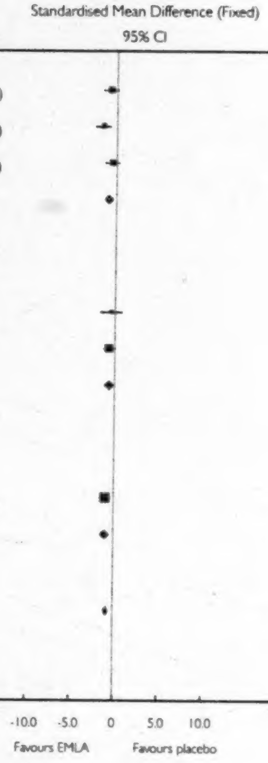
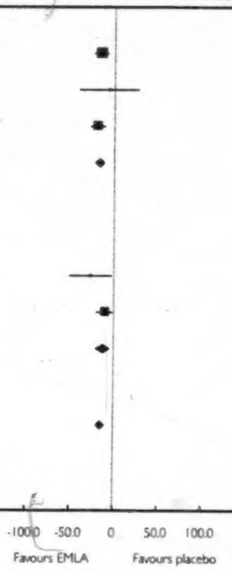


Fig. 19. Comparison 03 EMLA versus placebo or no treatment

03.03 Heart rate (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 03 EMLA versus placebo or no treatment
Outcome: 03 Heart rate (by unit)

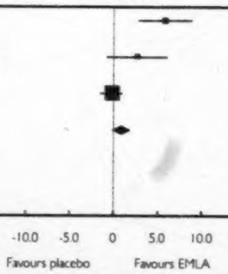


Study	EMLA N	EMLA Mean(SD)	Placebo or no tx N	Placebo or no tx Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 in bpm							
Benini 1993	14	148.45 (11.41)	13	162.87 (9.10)		37.4	-14.42 [-22.18, -6.66]
Joyce 2001	5	144.02 (16.03)	5	149.63 (35.78)		1.9	-5.61 [-39.98, 28.76]
Woodman 1999	20	137.36 (14.12)	21	155.53 (14.16)		30.0	-18.17 [-26.83, -9.51]
Subtotal (95% CI)	39		39			69.3	-15.80 [-21.50, -10.10]
Test for heterogeneity chi-square=0.75 df=2 p=0.69 I^2 =0.0%							
Test for overall effect z=5.44 p<0.00001							
02 in bpm change-from-baseline							
Lander 1997	15	20.60 (23.61)	12	46.70 (38.17)		3.7	-26.10 [-50.78, -1.42]
Taddio 1997	19	7.00 (13.00)	20	17.00 (16.00)		27.0	-10.00 [-19.13, -0.87]
Subtotal (95% CI)	34		32			30.7	-11.94 [-20.50, -3.38]
Test for heterogeneity chi-square=1.44 df=1 p=0.23 I^2 =30.5%							
Test for overall effect z=2.73 p=0.006							
Total (95% CI)	73		71			100.0	-14.62 [-19.36, -9.87]
Test for heterogeneity chi-square=2.73 df=4 p=0.60 I^2 =0.0%							
Test for overall effect z=6.04 p<0.00001							

Fig. 20. Comparison 03 EMLA versus placebo or no treatment

03.04 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 03 EMLA versus placebo or no treatment
Outcome: 04 Oxygen saturation (%)



Study	EMLA N	EMLA Mean(SD)	Placebo or no tx N	Placebo or no tx Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Benini 1993	14	92.05 (2.59)	13	86.15 (5.05)		12.8	5.90 [2.84, 8.96]
Joyce 2001	5	94.40 (3.22)	5	91.70 (2.18)		10.3	2.70 [-0.71, 6.11]
Woodman 1999	20	97.33 (1.91)	21	97.50 (2.17)		76.9	-0.17 [-1.42, 1.08]
Total (95% CI)	39		39			100.0	0.90 [-0.19, 2.00]
Test for heterogeneity chi-square=14.13 df=2 p=0.0009 I^2 =85.8%							
Test for overall effect z=1.62 p=0.1							

Fig. 21. Comparison 03 EMLA versus placebo or no treatment

03.05 Respiratory rate (rpm)

Review: Pain relief for neonatal circumcision
Comparison: 03 EMLA versus placebo or no treatment
Outcome: 05 Respiratory rate (rpm)

Study	EMLA N	EMLA Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Joyce 2001	5	48.13 (12.95)	5	52.44 (13.63)		100.0	-4.31 [-20.79, 12.17]
Total (95% CI)	5		5			100.0	-4.31 [-20.79, 12.17]

Test for heterogeneity: not applicable
Test for overall effect z=0.51 p=0.6

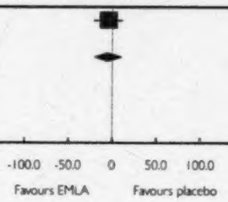


Fig. 22. Comparison 03 EMLA versus placebo or no treatment

03.06 Systolic blood pressure (mmHg) change-from-baseline

Review: Pain relief for neonatal circumcision
Comparison: 03 EMLA versus placebo or no treatment
Outcome: 06 Systolic blood pressure (mmHg) change-from-baseline

Study	EMLA N	EMLA Mean(SD)	Placebo or no tx N	Placebo or no tx Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Taddio 1997	22	11.00 (17.00)	16	14.00 (21.00)		100.0	-3.00 [-15.50, 9.50]
Total (95% CI)	22		16			100.0	-3.00 [-15.50, 9.50]

Test for heterogeneity: not applicable
Test for overall effect z=0.47 p=0.6

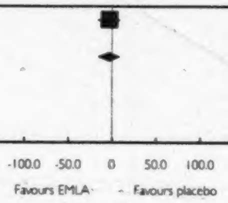


Fig. 23. Comparison 03 EMLA versus placebo or no treatment

03.07 Diastolic blood pressure (mmHg) change-from-baseline

Review: Pain relief for neonatal circumcision

Comparison: 03 EMLA versus placebo or no treatment

Outcome: 07 Diastolic blood pressure (mmHg) change-from-baseline

Study	EMLA N	EMLA Mean(SD)	Placebo or no tx N	Placebo or no tx Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Taddio 1997	22	19.00 (22.00)	16	24.00 (33.00)		100.0	-5.00 [-23.60, 13.60]
Total (95% CI)	22		16			100.0	-5.00 [-23.60, 13.60]

Test for heterogeneity: not applicable

Test for overall effect z=0.53 p=0.6

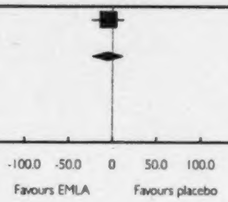


Fig. 24. Comparison 04 Topical lidocaine versus placebo

04.01 Pain score

Review: Pain relief for neonatal circumcision

Comparison: 04 Topical lidocaine versus placebo

Outcome: 01 Pain score

Study	Lidocaine N	Lidocaine Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 % change- from-baseline in time spent in Brazelton state 6 (full cry)							
Weatherstone 1993	12	7.00 (18.00)	13	15.00 (20.00)		100.0	-8.00 [-22.90, 6.90]
Subtotal (95% CI)	12		13			100.0	-8.00 [-22.90, 6.90]

Test for heterogeneity: not applicable

Test for overall effect z=1.05 p=0.3

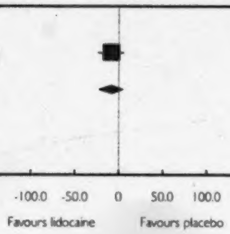


Fig. 25. Comparison 04 Topical lidocaine versus placebo

04.02 Cry time (s)

Review: Pain relief for neonatal circumcision
Comparison: 04 Topical lidocaine versus placebo
Outcome: 02 Cry time (s)

Study	Lidocaine N	Lidocaine Mean(SD)	Placebo N	Placebo Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Mudge 1989	20	195.00 (90.19)	24	263.00 (90.19)	54.2	-68.00 [-121.52, -14.48]
Woodman 1999	20	172.00 (80.67)	21	222.00 (108.07)	45.8	-50.00 [-108.19, 8.19]
Total (95% CI)	40		45		100.0	-59.75 [-99.14, -20.36]

Test for heterogeneity chi-square=0.20 df=1 p=0.66 I² =0.0%
Test for overall effect z=2.97 p=0.003

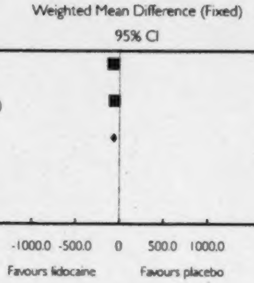


Fig. 26. Comparison 04 Topical lidocaine versus placebo

04.03 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 04 Topical lidocaine versus placebo
Outcome: 03 Heart rate (bpm)

Study	Lidocaine N	Lidocaine Mean(SD)	Placebo N	Placebo Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Mudge 1989	20	148.40 (9.75)	24	160.27 (14.16)	52.2	-11.87 [-18.97, -4.77]
Woodman 1999	20	149.25 (9.75)	21	155.53 (14.16)	47.8	-6.28 [-13.69, 1.13]
Total (95% CI)	40		45		100.0	-9.20 [-14.32, -4.07]

Test for heterogeneity chi-square=1.14 df=1 p=0.29 I² =12.3%
Test for overall effect z=3.52 p=0.0004

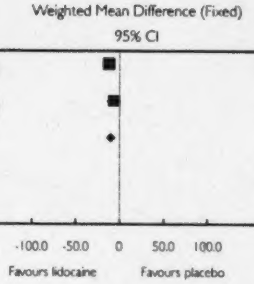


Fig. 27. Comparison 04 Topical lidocaine versus placebo

04.04 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 04 Topical lidocaine versus placebo
Outcome: 04 Oxygen saturation (%)

Study	Lidocaine		Placebo		Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	(%)	95% CI
× Mudge 1989	20	91.43 (0.00)	24	87.55 (0.00)	0.0	Not estimable
Woodman 1999	20	97.00 (1.91)	21	97.50 (2.17)	100.0	-0.50 [-1.75, 0.75]
Total (95% CI)	40		45		100.0	-0.50 [-1.75, 0.75]

Test for heterogeneity: not applicable
Test for overall effect z=0.78 p=0.4

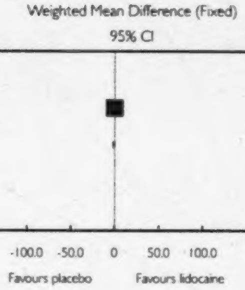


Fig. 28. Comparison 04 Topical lidocaine versus placebo

04.05 Respiratory rate (rpm)

Review: Pain relief for neonatal circumcision
Comparison: 04 Topical lidocaine versus placebo
Outcome: 05 Respiratory rate (rpm)

Study	Lidocaine		Placebo		Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	(%)	95% CI
× Mudge 1989	20	41.53 (0.00)	24	44.65 (0.00)	0.0	Not estimable

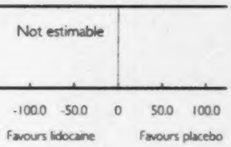
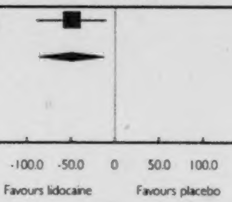


Fig. 29. Comparison 04 Topical lidocaine versus placebo

04.06 B-endorphin (pg/mL)

Review: Pain relief for neonatal circumcision
Comparison: 04 Topical lidocaine versus placebo
Outcome: 06 B-endorphin (pg/mL)

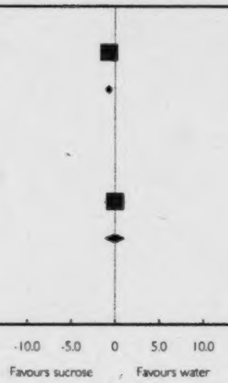


Study	lidocaine		placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Weatherstone 1993	15	65.00 (57.00)	15	114.00 (54.00)		100.0	-49.00 [-88.73, -9.27]
Total (95% CI)	15		15			100.0	-49.00 [-88.73, -9.27]
Test for heterogeneity: not applicable							
Test for overall effect z=2.42 p=0.02							

Fig. 30. Comparison 05 Sucrose versus water or no treatment

05.01 Pain score

Review: Pain relief for neonatal circumcision
Comparison: 05 Sucrose versus water or no treatment
Outcome: 01 Pain score



Study	Sucrose		Water		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 behavioral distress score							
Stang 1997	20	0.45 (0.80)	20	1.12 (0.48)		100.0	-0.67 [-1.08, -0.26]
Subtotal (95% CI)	20		20			100.0	-0.67 [-1.08, -0.26]
Test for heterogeneity: not applicable							
Test for overall effect z=3.21 p=0.001							
02 modified behavioral pain scale (MBPS)							
Kass 2001	23	7.63 (2.13)	24	7.63 (1.73)		100.0	0.00 [-1.11, 1.11]
Subtotal (95% CI)	23		24			100.0	0.00 [-1.11, 1.11]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							

Fig. 31. Comparison 05 Sucrose versus water or no treatment

05.02 Cry time (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 05 Sucrose versus water or no treatment
Outcome: 02 Cry time (by unit)

Study	Sucrose N	Sucrose Mean(SD)	Water N	Water Mean(SD)	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 in %						
Blass 1991 A	5	29.20 (18.66)	10	48.00 (18.97)	10.8	-0.94 [-2.08, 0.20]
Blass 1991 B	5	29.20 (18.66)	10	66.50 (11.07)	6.2	-2.53 [-4.04, -1.03]
Zahorodny 1998	13	76.00 (18.66)	13	76.00 (18.97)	23.9	0.00 [-0.77, 0.77]
Subtotal (95% CI)	23		33		41.0	-0.63 [-1.22, -0.05]
Test for heterogeneity chi-square=9.00 df=2 p=0.01 I² =77.8%						
Test for overall effect z=2.11 p=0.03						
02 in seconds						
Kass 2001	24	256.00 (68.00)	23	225.00 (39.00)	41.5	0.55 [-0.04, 1.13]
Zolnoski 1993	10	279.80 (84.07)	10	242.00 (35.31)	17.5	0.56 [-0.34, 1.46]
Subtotal (95% CI)	34		33		59.0	0.55 [0.06, 1.04]
Test for heterogeneity chi-square=0.00 df=1 p=0.98 I² =0.0%						
Test for overall effect z=2.21 p=0.03						
Total (95% CI)	57		66		100.0	0.07 [-0.31, 0.44]
Test for heterogeneity chi-square=18.22 df=4 p=0.001 I² =78.0%						
Test for overall effect z=0.34 p=0.7						

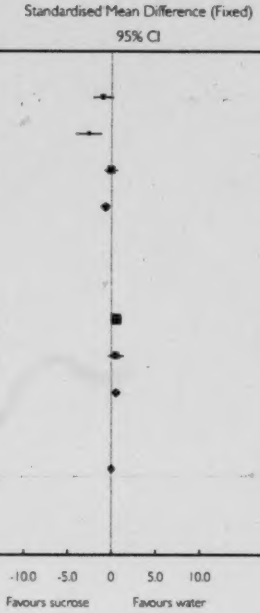


Fig. 32. Comparison 05 Sucrose versus water or no treatment

05.03 Heart rate (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 05 Sucrose versus water or no treatment

Outcome: 03 Heart rate (by unit)

Study	Sucrose N	Sucrose Mean(SD)	Water or no tx N	Water or no tx Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 in bpm						
Kass 2001	23	182.11 (22.03)	24	178.76 (23.14)	18.3	3.35 [-9.56, 16.26]
Zolnoski 1993	10	172.53 (10.72)	10	171.00 (10.80)	34.3	1.53 [-7.90, 10.96]
Subtotal (95% CI)	33		34		52.6	2.16 [-5.45, 9.78]
Test for heterogeneity chi-square=0.05 df=1 p=0.82 I^2 =0.0%						
Test for overall effect z=0.56 p=0.6						
02 in bpm change-from-baseline						
Herschel 1998	39	27.10 (19.20)	40	36.80 (17.10)	47.4	-9.70 [-17.72, -1.68]
Subtotal (95% CI)	39		40		47.4	-9.70 [-17.72, -1.68]
Test for heterogeneity: not applicable						
Test for overall effect z=2.37 p=0.02						
Total (95% CI)	72		74		100.0	-3.46 [-8.98, 2.07]
Test for heterogeneity chi-square=4.47 df=2 p=0.11 I^2 =55.2%						
Test for overall effect z=1.23 p=0.2						

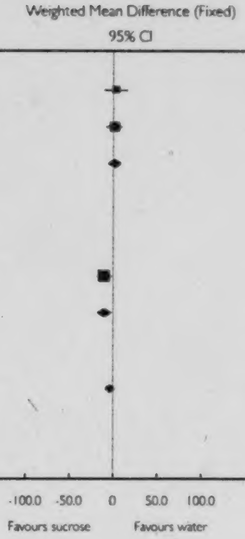


Fig. 33. Comparison 05 Sucrose versus water or no treatment

05.04 Oxygen saturation (by unit)

Review: Pain relief for neonatal circumcision

Comparison: 05 Sucrose versus water or no treatment

Outcome: 04 Oxygen saturation (by unit)

Study	Sucrose		Water or no tx		Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	(%)	95% CI
01 in %						
Kass 2001	23	94.35 (3.80)	24	95.18 (4.02)	34.2	-0.83 [-3.07, 1.41]
Subtotal (95% CI)	23		24		34.2	-0.83 [-3.07, 1.41]
Test for heterogeneity: not applicable						
Test for overall effect z=0.73 p=0.5						
02 in % change-from-baseline						
Herschel 1998	39	0.70 (3.40)	40	-2.50 (3.90)	65.8	3.20 [1.59, 4.81]
Subtotal (95% CI)	39		40		65.8	3.20 [1.59, 4.81]
Test for heterogeneity: not applicable						
Test for overall effect z=3.89 p=0.0001						
Total (95% CI)	62		64		100.0	1.82 [0.51, 3.13]
Test for heterogeneity chi-square=8.21 df=1 p=0.004 I² =87.8%						
Test for overall effect z=2.73 p=0.006						

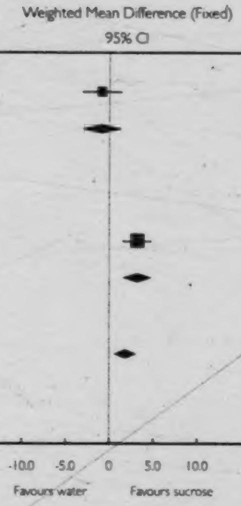


Fig. 34. Comparison 05 Sucrose versus water or no treatment

05.05 Serum cortisol (nmol/dL) 30 min post

Review: Pain relief for neonatal circumcision

Comparison: 05 Sucrose versus water or no treatment

Outcome: 05 Serum cortisol (nmol/dL) 30 min post

Study	Sucrose		Water		Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	(%)	95% CI
Stang 1997	20	441.10 (217.80)	20	372.20 (176.40)	100.0	68.90 [-53.93, 191.73]
Total (95% CI)	20		20		100.0	68.90 [-53.93, 191.73]
Test for heterogeneity: not applicable						
Test for overall effect z=1.10 p=0.3						

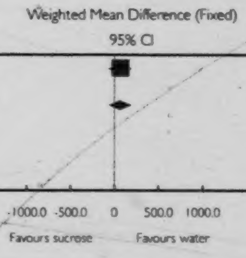


Fig. 35. Comparison 06 Acetaminophen versus placebo

06.01 Pain / behavior score

Review: Pain relief for neonatal circumcision
Comparison: 06 Acetaminophen versus placebo
Outcome: 01 Pain / behavior score

Study	Acetaminophen		Placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 comfort score - change from baseline score at 30 min post							
Howard 1994	23	-3.50 (2.20)	21	-3.70 (2.60)		100.0	0.20 [-1.23, 1.63]
Subtotal (95% CI)	23		21			100.0	0.20 [-1.23, 1.63]
Test for heterogeneity: not applicable							
Test for overall effect z=0.27 p=0.8							
02 Nursing Child Assessment Feeding Scale (NCAFS) - total infant score							
Macke 2001	29	16.40 (6.28)	31	12.40 (5.72)		100.0	4.00 [0.95, 7.05]
Subtotal (95% CI)	29		31			100.0	4.00 [0.95, 7.05]
Test for heterogeneity: not applicable							
Test for overall effect z=2.57 p=0.01							

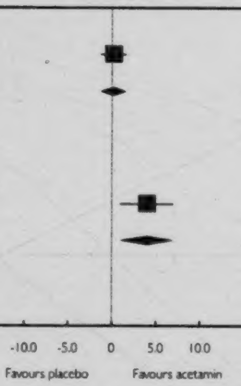


Fig. 36. Comparison 06 Acetaminophen versus placebo

06.02 Cry time (%)

Review: Pain relief for neonatal circumcision
Comparison: 06 Acetaminophen versus placebo
Outcome: 02 Cry time (%)

Study	Acetaminophen		Placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Howard 1994	23	60.25 (16.47)	21	67.00 (18.95)		38.0	-6.75 [-17.29, 3.79]
Macke 2001	29	70.40 (16.30)	31	69.10 (16.30)		62.0	1.30 [-6.95, 9.55]
Total (95% CI)	52		52			100.0	-1.76 [-8.26, 4.74]
Test for heterogeneity chi-square=1.39 df=1 p=0.24 I² =28.0%							
Test for overall effect z=0.53 p=0.6							

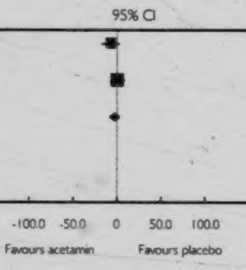


Fig. 37. Comparison 06 Acetaminophen versus placebo

06.03 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 06 Acetaminophen versus placebo
Outcome: 03 Heart rate (bpm)

Study	Acetaminophen		Placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Howard 1994	23	152.12 (15.36)	21	149.45 (16.10)		30.7	2.67 [-6.65, 11.99]
Macke 2001	29	166.10 (12.10)	31	164.00 (12.40)		69.3	2.10 [-4.10, 8.30]
Total (95% CI)	52		52			100.0	2.27 [-2.89, 7.44]

Test for heterogeneity chi-square=0.01 df=1 p=0.92 I^2 =0.0%
Test for overall effect z=0.86 p=0.4

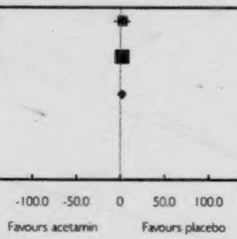


Fig. 38. Comparison 06 Acetaminophen versus placebo

06.04 Respiratory rate (rpm)

Review: Pain relief for neonatal circumcision
Comparison: 06 Acetaminophen versus placebo
Outcome: 04 Respiratory rate (rpm)

Study	Acetaminophen		Placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Howard 1994	23	54.27 (10.54)	21	58.00 (13.69)		100.0	-3.73 [-11.00, 3.54]
Total (95% CI)	23		21			100.0	-3.73 [-11.00, 3.54]

Test for heterogeneity: not applicable
Test for overall effect z=1.01 p=0.3

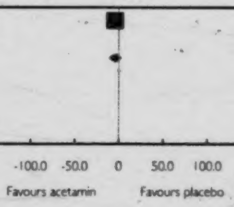


Fig. 39. Comparison 07 DPNB versus EMLA

07.01 Pain score

Review: Pain relief for neonatal circumcision
Comparison: 07 DPNB versus EMLA
Outcome: 01 Pain score

Study	DPNB N	DPNB Mean(SD)	EMLA N	EMLA Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 neonatal infant pain scale (NIPS)							
Butler O'Hara 1998	23	2.30 (1.80)	21	4.80 (0.70)		100.0	-2.50 [-3.29, -1.71]
Subtotal (95% CI)	23		21			100.0	-2.50 [-3.29, -1.71]
Test for heterogeneity: not applicable							
Test for overall effect z=6.17 p<0.00001							
02 behavioral distress score							
Howard 1999	29	1.22 (0.48)	31	1.50 (0.50)		100.0	-0.28 [-0.53, -0.03]
Subtotal (95% CI)	29		31			100.0	-0.28 [-0.53, -0.03]
Test for heterogeneity: not applicable							
Test for overall effect z=2.21 p=0.03							

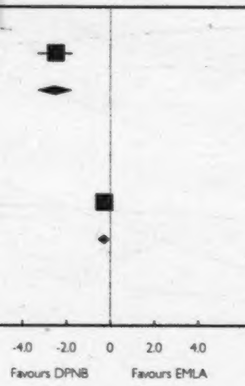


Fig. 40. Comparison 07 DPNB versus EMLA

07.02 Cry time (%)

Review: Pain relief for neonatal circumcision
Comparison: 07 DPNB versus EMLA
Outcome: 02 Cry time (%)

Study	DPNB N	DPNB Mean(SD)	EMLA N	EMLA Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Lander 1997	14	47.33 (29.97)	15	57.33 (23.66)		100.0	-10.00 [-29.74, 9.74]
Total (95% CI)	14		15			100.0	-10.00 [-29.74, 9.74]
Test for heterogeneity: not applicable							
Test for overall effect z=0.99 p=0.3							

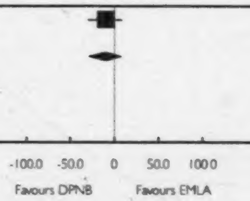
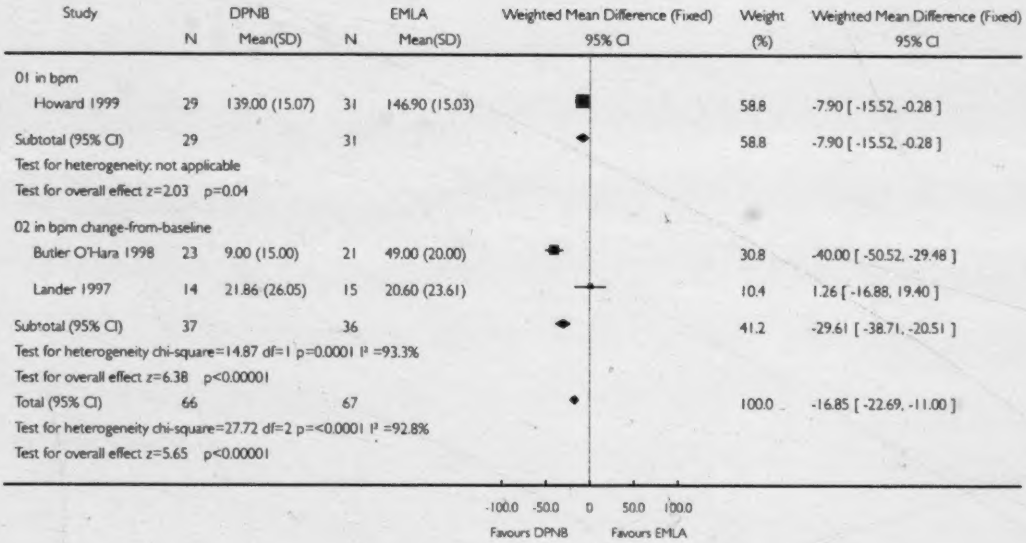


Fig. 41. Comparison 07 DPNB versus EMLA

07.03 Heart rate (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 07 DPNB versus EMLA
Outcome: 03 Heart rate (by unit)



Study	DPNB		EMLA		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 in bpm							
Howard 1999	29	139.00 (15.07)	31	146.90 (15.03)		58.8	-7.90 [-15.52, -0.28]
Subtotal (95% CI)	29		31			58.8	-7.90 [-15.52, -0.28]
Test for heterogeneity: not applicable							
Test for overall effect z=2.03 p=0.04							
02 in bpm change-from-baseline							
Butler O'Hara 1998	23	9.00 (15.00)	21	49.00 (20.00)		30.8	-40.00 [-50.52, -29.48]
Lander 1997	14	21.86 (26.05)	15	20.60 (23.61)		10.4	1.26 [-16.88, 19.40]
Subtotal (95% CI)	37		36			41.2	-29.61 [-38.71, -20.51]
Test for heterogeneity chi-square=14.87 df=1 p=0.0001 I^2 =93.3%							
Test for overall effect z=6.38 p<0.00001							
Total (95% CI)	66		67			100.0	-16.85 [-22.69, -11.00]
Test for heterogeneity chi-square=27.72 df=2 p=<0.0001 I^2 =92.8%							
Test for overall effect z=5.65 p<0.00001							

Fig. 42. Comparison 07 DPNB versus EMLA

07.04 Heart rate by wait time

Review: Pain relief for neonatal circumcision

Comparison: 07 DPNB versus EMLA

Outcome: 04 Heart rate by wait time

Study	DPNB N	DPNB Mean(SD)	EMLA N	EMLA Mean(SD)	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 wait time after anesthetic administration </= 5 min						
Butler O'Hara 1998	23	9.00 (15.00)	21	49.00 (20.00)	31.0	-2.24 [-3.01, -1.47]
Howard 1999	29	139.00 (15.07)	31	146.90 (15.03)	69.0	-0.52 [-1.03, 0.00]
Subtotal (95% CI)	52		52		100.0	-1.05 [-1.48, -0.62]
Test for heterogeneity chi-square=13.27 df=1 p=0.0003 I² =92.5%						
Test for overall effect z=4.82 p<0.00001						
02 wait time after anesthetic administration > 5 min						
Lander 1997	14	21.86 (26.05)	15	20.60 (23.61)	100.0	0.05 [-0.68, 0.78]
Subtotal (95% CI)	14		15		100.0	0.05 [-0.68, 0.78]
Test for heterogeneity: not applicable						
Test for overall effect z=0.13 p=0.9						

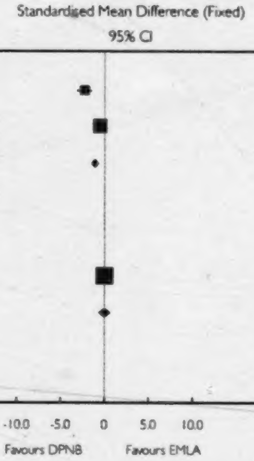


Fig. 43. Comparison 07 DPNB versus EMLA

07.05 Respiratory rate (rpm)

Review: Pain relief for neonatal circumcision

Comparison: 07 DPNB versus EMLA

Outcome: 05 Respiratory rate (rpm)

Study	DPNB N	DPNB Mean(SD)	EMLA N	EMLA Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Howard 1999	29	53.40 (9.15)	31	56.30 (8.90)	100.0	-2.90 [-7.47, 1.67]
Total (95% CI)	29		31		100.0	-2.90 [-7.47, 1.67]
Test for heterogeneity: not applicable						
Test for overall effect z=1.24 p=0.2						

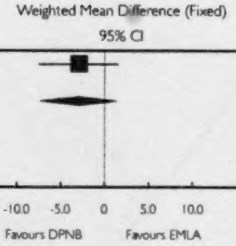


Fig. 44. Comparison 08 DPNB versus sucrose

08.01 Pain score

Review: Pain relief for neonatal circumcision
Comparison: 08 DPNB versus sucrose
Outcome: 01 Pain score

Study	DPNB N	DPNB Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 modified behavioral pain scale							
Kass 2001	24	4.40 (2.80)	23	7.63 (2.13)		100.0	-3.23 [-4.65, -1.81]
Total (95% CI)	24		23			100.0	-3.23 [-4.65, -1.81]
Test for heterogeneity: not applicable							
Test for overall effect z=4.46 p<0.00001							

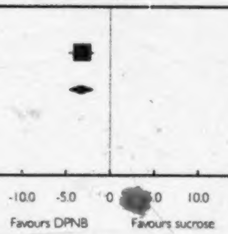


Fig. 45. Comparison 08 DPNB versus sucrose

08.02 Cry time (s)

Review: Pain relief for neonatal circumcision
Comparison: 08 DPNB versus sucrose
Outcome: 02 Cry time (s)

Study	DPNB N	DPNB Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Kass 2001	24	90.00 (87.00)	23	256.00 (68.00)		100.0	-166.00 [-210.54, -121.46]
Total (95% CI)	24		23			100.0	-166.00 [-210.54, -121.46]
Test for heterogeneity: not applicable							
Test for overall effect z=7.30 p<0.00001							

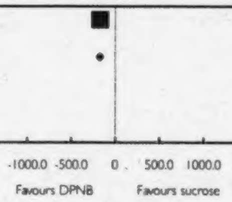
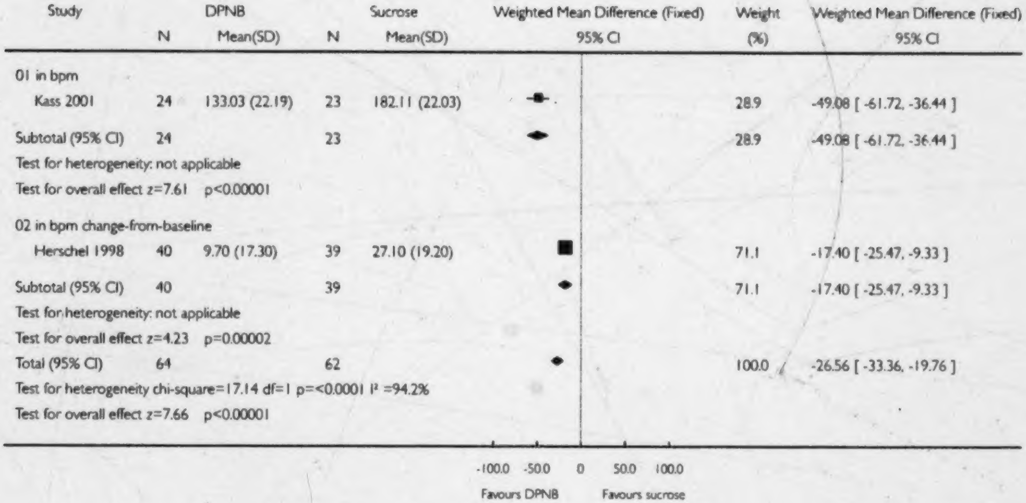


Fig. 46. Comparison 08 DPNB versus sucrose

08.03 Heart rate (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 08 DPNB versus sucrose
Outcome: 03 Heart rate (by unit)



Study	DPNB N	DPNB Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 in bpm						
Kass 2001	24	133.03 (22.19)	23	182.11 (22.03)	28.9	-49.08 [-61.72, -36.44]
Subtotal (95% CI)	24		23		28.9	-49.08 [-61.72, -36.44]
Test for heterogeneity: not applicable						
Test for overall effect z=7.61 p<0.00001						
02 in bpm change-from-baseline						
Herschel 1998	40	9.70 (17.30)	39	27.10 (19.20)	71.1	-17.40 [-25.47, -9.33]
Subtotal (95% CI)	40		39		71.1	-17.40 [-25.47, -9.33]
Test for heterogeneity: not applicable						
Test for overall effect z=4.23 p=0.00002						
Total (95% CI)	64		62		100.0	-26.56 [-33.36, -19.76]
Test for heterogeneity chi-square=17.14 df=1 p=<0.0001 I² =94.2%						
Test for overall effect z=7.66 p<0.00001						

Fig. 47. Comparison 08 DPNB versus sucrose

08.04 Oxygen saturation (by unit)

Review: Pain relief for neonatal circumcision
Comparison: 08 DPNB versus sucrose
Outcome: 04 Oxygen saturation (by unit)

Study	DPNB N	DPNB Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 in %						
Kass 2001	24	98.20 (2.24)	23	94.35 (3.80)	32.7	3.85 [2.06, 5.64]
Subtotal (95% CI)	24		23		32.7	3.85 [2.06, 5.64]
Test for heterogeneity: not applicable						
Test for overall effect z=4.21 p=0.00003						
02 in % change-from-baseline						
Herschel 1998	40	-0.80 (2.10)	39	0.70 (3.40)	67.3	-1.50 [-2.75, -0.25]
Subtotal (95% CI)	40		39		67.3	-1.50 [-2.75, -0.25]
Test for heterogeneity: not applicable						
Test for overall effect z=2.35 p=0.02						
Total (95% CI)	64		62		100.0	0.25 [-0.78, 1.27]
Test for heterogeneity chi-square=23.02 df=1 p=<0.0001 I^2 =95.7%						
Test for overall effect z=0.48 p=0.6						

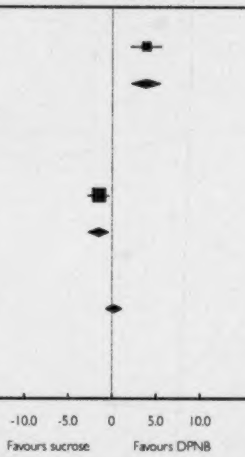


Fig. 48. Comparison 09 DPNB versus ring block

09.01 Cry time (%)

Review: Pain relief for neonatal circumcision
Comparison: 09 DPNB versus ring block
Outcome: 01 Cry time (%)

Study	DPNB N	DPNB Mean(SD)	RB N	RB Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Lander 1997	14	47.33 (29.97)	13	41.00 (27.91)	100.0	6.33 [-15.50, 28.16]
Total (95% CI)	14		13		100.0	6.33 [-15.50, 28.16]
Test for heterogeneity: not applicable						
Test for overall effect z=0.57 p=0.6						

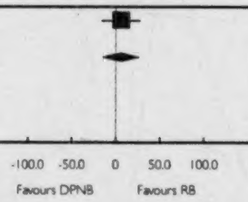


Fig. 49. Comparison 09 DPNB versus ring block

09.02 Heart rate (bpm) change-from-baseline

Review: Pain relief for neonatal circumcision
Comparison: 09 DPNB versus ring block
Outcome: 02 Heart rate (bpm) change-from-baseline

Study	DPNB N	DPNB Mean(SD)	RB N	RB Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Lander 1997	14	21.86 (26.05)	13	17.43 (22.99)		100.0	4.43 [-14.07, 22.93]
Total (95% CI)	14		13			100.0	4.43 [-14.07, 22.93]

Test for heterogeneity: not applicable
Test for overall effect z=0.47 p=0.6

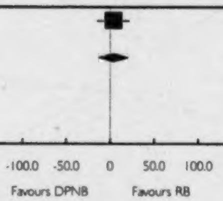


Fig. 50. Comparison 10 DPNB versus local block

10.01 Serum cortisol (nmol/dL) 30 min post

Review: Pain relief for neonatal circumcision
Comparison: 10 DPNB versus local block
Outcome: 01 Serum cortisol (nmol/dL) 30 min post

Study	DPNB N	DPNB Mean(SD)	Local N	Local Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Masciello 1990	9	721.27 (159.47)	9	415.00 (195.72)		100.0	306.27 [141.33, 471.21]
Total (95% CI)	9		9			100.0	306.27 [141.33, 471.21]

Test for heterogeneity: not applicable
Test for overall effect z=3.64 p=0.0003

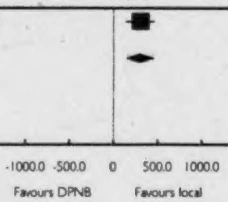


Fig. 51. Comparison 11 Ring block versus EMLA

11.01 Heart rate (bpm) change-from-baseline

Review: Pain relief for neonatal circumcision
Comparison: 11 Ring block versus EMLA
Outcome: 01 Heart rate (bpm) change-from-baseline

Study	Ring block N	Ring block Mean(SD)	EMLA N	EMLA Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Lander 1997	13	17.43 (22.99)	15	20.60 (23.62)		100.0	-3.17 [-20.46, 14.12]
Total (95% CI)	13		15			100.0	-3.17 [-20.46, 14.12]

Test for heterogeneity: not applicable
Test for overall effect z=0.36 p=0.7

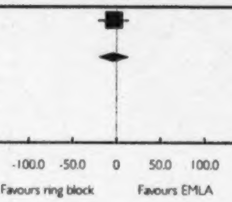


Fig. 52. Comparison 11 Ring block versus EMLA

11.02 Cry time (%)

Review: Pain relief for neonatal circumcision
Comparison: 11 Ring block versus EMLA
Outcome: 02 Cry time (%)

Study	Ring block N	Ring block Mean(SD)	EMLA N	EMLA Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Lander 1997	13	41.00 (27.91)	15	57.33 (23.66)		100.0	-16.33 [-35.66, 3.00]
Total (95% CI)	13		15			100.0	-16.33 [-35.66, 3.00]

Test for heterogeneity: not applicable
Test for overall effect z=1.66 p=0.1

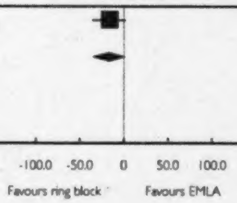


Fig. 53. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

12.01 Pain score

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome: 01 Pain score

Study	Buffered lidocaine N	Mean(SD)	Plain lidocaine N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 behavioral distress score							
Stang 1997	20	1.22 (0.78)	20	1.12 (0.48)		100.0	0.10 [-0.30, 0.50]
Subtotal (95% CI)	20		20			100.0	0.10 [-0.30, 0.50]
Test for heterogeneity: not applicable							
Test for overall effect z=0.49 p=0.6							

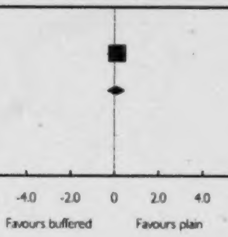


Fig. 54. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

12.02 Cry time (%)

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome: 02 Cry time (%)

Study	Buffered lidocaine N	Mean(SD)	Plain lidocaine N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Newton 1999	102	65.00 (74.00)	92	56.00 (73.00)		100.0	9.00 [-11.71, 29.71]
Total (95% CI)	102		92			100.0	9.00 [-11.71, 29.71]
Test for heterogeneity: not applicable							
Test for overall effect z=0.85 p=0.4							

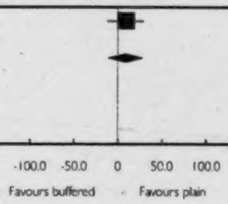
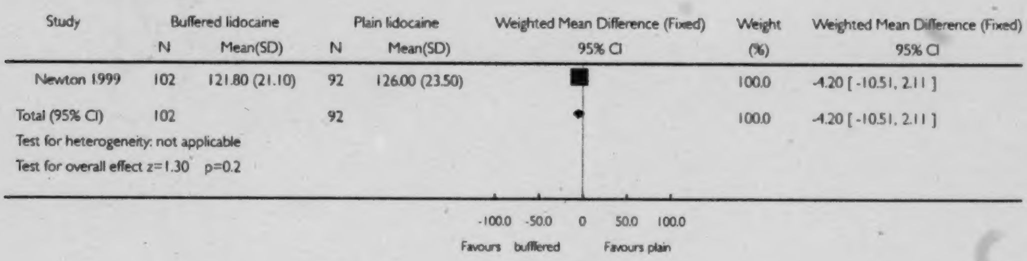


Fig. 55. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

12.03 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB
Outcome: 03 Heart rate (bpm)



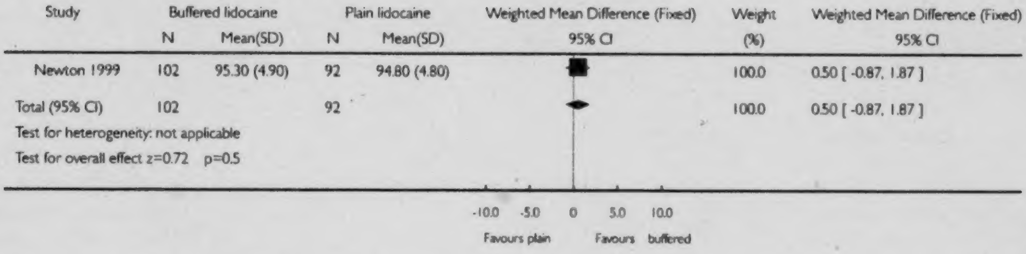
Study	Buffered lidocaine N	Buffered lidocaine Mean(SD)	Plain lidocaine N	Plain lidocaine Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Newton 1999	102	121.80 (21.10)	92	126.00 (23.50)	100.0	-4.20 [-10.51, 2.11]
Total (95% CI)	102		92		100.0	-4.20 [-10.51, 2.11]

Test for heterogeneity: not applicable
Test for overall effect z=1.30 p=0.2

Fig. 56. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

12.04 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB
Outcome: 04 Oxygen saturation (%)



Study	Buffered lidocaine N	Buffered lidocaine Mean(SD)	Plain lidocaine N	Plain lidocaine Mean(SD)	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Newton 1999	102	95.30 (4.90)	92	94.80 (4.80)	100.0	0.50 [-0.87, 1.87]
Total (95% CI)	102		92		100.0	0.50 [-0.87, 1.87]

Test for heterogeneity: not applicable
Test for overall effect z=0.72 p=0.5

Fig. 57. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

12.05 Serum cortisol (nmol/dL) 30 min post

Review: Pain relief for neonatal circumcision
Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB
Outcome: 05 Serum cortisol (nmol/dL) 30 min post

Study	Buffered lidocaine		Plain lidocaine		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Stang 1997	20	408.00 (270.20)	20	372.20 (176.40)		100.0	35.80 [-105.62, 177.22]
Total (95% CI)	20		20			100.0	35.80 [-105.62, 177.22]

Test for heterogeneity: not applicable
Test for overall effect z=0.50 p=0.6

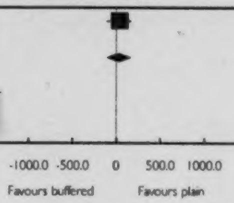


Fig. 58. Comparison 13 EMLA versus 30% topical lidocaine

13.01 Cry time (s)

Review: Pain relief for neonatal circumcision
Comparison: 13 EMLA versus 30% topical lidocaine
Outcome: 01 Cry time (s)

Study	EMLA		Lidocaine		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Woodman 1999	20	155.00 (104.91)	20	172.00 (80.68)		100.0	-17.00 [-75.00, 41.00]
Total (95% CI)	20		20			100.0	-17.00 [-75.00, 41.00]

Test for heterogeneity: not applicable
Test for overall effect z=0.57 p=0.6

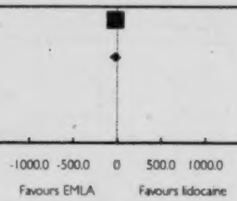


Fig. 59. Comparison 13 EMLA versus 30% topical lidocaine

13.02 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 13 EMLA versus 30% topical lidocaine
Outcome: 02 Heart rate (bpm)

Study	EMLA		Lidocaine		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Woodman 1999	20	137.37 (14.12)	20	149.25 (9.75)		100.0	-11.88 [-19.40, -4.36]
Total (95% CI)	20		20			100.0	-11.88 [-19.40, -4.36]

Test for heterogeneity: not applicable
Test for overall effect z=3.10 p=0.002

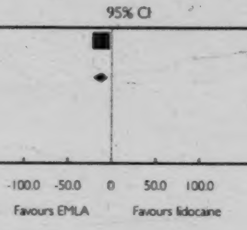


Fig. 60. Comparison 13 EMLA versus 30% topical lidocaine

13.03 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 13 EMLA versus 30% topical lidocaine
Outcome: 03 Oxygen saturation (%)

Study	EMLA		Lidocaine		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Woodman 1999	20	97.33 (1.91)	20	97.50 (2.17)		100.0	-0.17 [-1.44, 1.10]
Total (95% CI)	20		20			100.0	-0.17 [-1.44, 1.10]

Test for heterogeneity: not applicable
Test for overall effect z=0.26 p=0.8

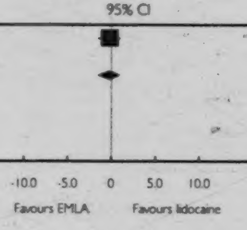


Fig. 61. Comparison 14 EMLA versus sucrose

14.01 Cry time (%)

Review: Pain relief for neonatal circumcision
Comparison: 14 EMLA versus sucrose
Outcome: 01 Cry time (%)

Study	EMLA N	EMLA Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Zahorodny 1998	13	66.00 (24.50)	13	76.00 (18.66)		100.0	-10.00 [-26.74, 6.74]
Total (95% CI)	13		13			100.0	-10.00 [-26.74, 6.74]

Test for heterogeneity: not applicable
Test for overall effect z=1.17 p=0.2

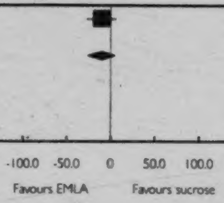


Fig. 62. Comparison 14 EMLA versus sucrose

14.02 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 14 EMLA versus sucrose
Outcome: 02 Heart rate (bpm)

Study	EMLA N	EMLA Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Mohan 1998	20	147.88 (15.86)	21	157.23 (19.12)		100.0	-9.35 [-20.08, 1.38]
Total (95% CI)	20		21			100.0	-9.35 [-20.08, 1.38]

Test for heterogeneity: not applicable
Test for overall effect z=1.71 p=0.09

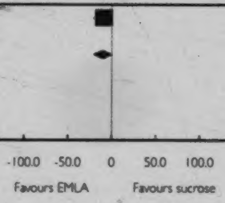


Fig. 63. Comparison 14 EMLA versus sucrose

14.03 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 14 EMLA versus sucrose
Outcome: 03 Oxygen saturation (%)

Study	EMLA		Sucrose		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Mohan 1998	20	95.38 (2.28)	21	96.20 (3.52)		100.0	-0.82 [-2.63, 0.99]
Total (95% CI)	20		21			100.0	-0.82 [-2.63, 0.99]

Test for heterogeneity: not applicable
Test for overall effect z=0.89 p=0.4

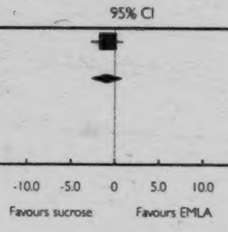


Fig. 64. Comparison 14 EMLA versus sucrose

14.04 Systolic blood pressure (mmHg)

Review: Pain relief for neonatal circumcision
Comparison: 14 EMLA versus sucrose
Outcome: 04 Systolic blood pressure (mmHg)

Study	EMLA		Sucrose		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
× Mohan 1998	20	71.78 (17.00)	21	83.50 (0.00)		0.0	Not estimable
Total (95% CI)	20		21			0.0	Not estimable

Test for heterogeneity: not applicable
Test for overall effect: not applicable

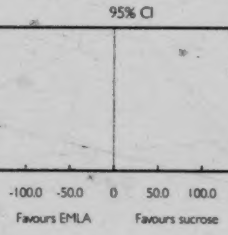


Fig. 65. Comparison 14 EMLA versus sucrose

14.05 Diastolic blood pressure (mmHg)

Review: Pain relief for neonatal circumcision
Comparison: 14 EMLA versus sucrose
Outcome: 05 Diastolic blood pressure (mmHg)

Study	EMLA N	EMLA Mean(SD)	Sucrose N	Sucrose Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
x Mohan 1998	20	43.05 (22.00)	21	51.95 (0.00)		0.0	Not estimable
Total (95% CI)	20		21			0.0	Not estimable

Test for heterogeneity: not applicable
Test for overall effect: not applicable

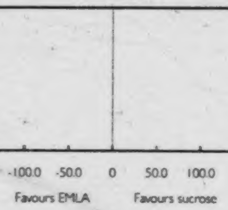


Fig. 66. Comparison 15 EMLA versus music

15.01 Cry time (min)

Review: Pain relief for neonatal circumcision
Comparison: 15 EMLA versus music
Outcome: 01 Cry time (min)

Study	EMLA N	EMLA Mean(SD)	Music N	Music Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Joyce 2001	5	7.80 (2.77)	7	7.42 (4.39)		100.0	0.38 [-3.68, 4.44]
Total (95% CI)	5		7			100.0	0.38 [-3.68, 4.44]

Test for heterogeneity: not applicable
Test for overall effect z=0.18 p=0.9

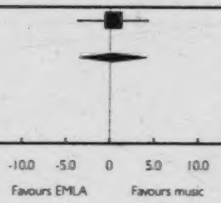
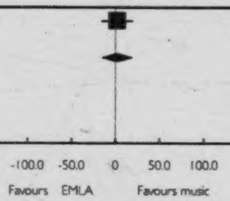


Fig. 67. Comparison 15 EMLA versus music

15.02 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 15 EMLA versus music
Outcome: 02 Heart rate (bpm)

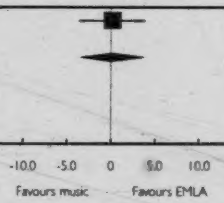
Study	EMLA		Music		Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
	N	Mean(SD)	N	Mean(SD)			
Joyce 2001	5	144.02 (16.03)	7	141.71 (15.82)		100.0	2.31 [-15.99, 20.61]
Total (95% CI)	5		7			100.0	2.31 [-15.99, 20.61]

Test for heterogeneity: not applicable
Test for overall effect z=0.25 p=0.8

Fig. 68. Comparison 15 EMLA versus music

15.03 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 15 EMLA versus music
Outcome: 03 Oxygen saturation (%)

Study	EMLA		Music		Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
	N	Mean(SD)	N	Mean(SD)			
Joyce 2001	5	94.40 (3.22)	7	94.21 (3.33)		100.0	0.19 [-3.56, 3.94]
Total (95% CI)	5		7			100.0	0.19 [-3.56, 3.94]

Test for heterogeneity: not applicable
Test for overall effect z=0.10 p=0.9

Fig. 69. Comparison 15 EMLA versus music

15.04 Respiratory rate (rpm)

Review: Pain relief for neonatal circumcision
Comparison: 15 EMLA versus music
Outcome: 04 Respiratory rate (rpm)

Study	EMLA		Music		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Joyce 2001	5	48.13 (12.95)	7	46.61 (13.49)		100.0	1.52 [-13.60, 16.64]
Total (95% CI)	5		7			100.0	1.52 [-13.60, 16.64]

Test for heterogeneity: not applicable
Test for overall effect z=0.20 p=0.8

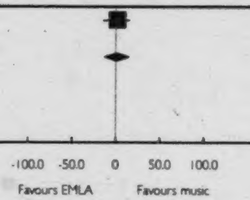


Fig. 70. Comparison 16 Music versus no treatment

16.01 Cry time (min)

Review: Pain relief for neonatal circumcision
Comparison: 16 Music versus no treatment
Outcome: 01 Cry time (min)

Study	Music		No music		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Joyce 2001	7	7.42 (4.39)	5	9.00 (3.08)		100.0	-1.58 [-5.81, 2.65]
Total (95% CI)	7		5			100.0	-1.58 [-5.81, 2.65]

Test for heterogeneity: not applicable
Test for overall effect z=0.73 p=0.5

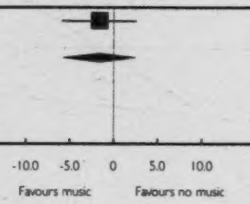


Fig. 71. Comparison 16 Music versus no treatment

16.02 Heart rate (bpm)

Review: Pain relief for neonatal circumcision
Comparison: 16 Music versus no treatment
Outcome: 02 Heart rate (bpm)

Study	Music		No music		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Joyce 2001	7	141.71 (15.82)	5	149.60 (35.78)		100.0	-7.89 [-41.37, 25.59]
Total (95% CI)	7		5			100.0	-7.89 [-41.37, 25.59]

Test for heterogeneity: not applicable
Test for overall effect z=0.46 p=0.6

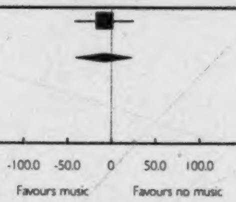


Fig. 72. Comparison 16 Music versus no treatment

16.03 Oxygen saturation (%)

Review: Pain relief for neonatal circumcision
Comparison: 16 Music versus no treatment
Outcome: 03 Oxygen saturation (%)

Study	Music		No music		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Joyce 2001	7	94.21 (3.33)	5	91.70 (2.19)		100.0	2.51 [-0.62, 5.64]
Total (95% CI)	7		5			100.0	2.51 [-0.62, 5.64]

Test for heterogeneity: not applicable
Test for overall effect z=1.57 p=0.1

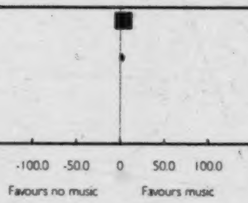


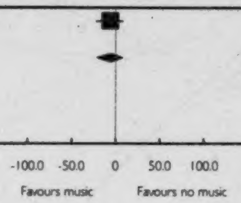
Fig. 73. Comparison 16 Music versus no treatment

16.04 Respiratory rate (rpm)

Review: Pain relief for neonatal circumcision
Comparison: 16 Music versus no treatment
Outcome: 04 Respiratory rate (rpm)

Study	Music N	Music Mean(SD)	No music N	No music Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Joyce 2001	7	46.61 (13.49)	5	52.44 (13.63)		100.0	-5.83 [-21.41, 9.75]
Total (95% CI)	7		5			100.0	-5.83 [-21.41, 9.75]

Test for heterogeneity: not applicable
Test for overall effect z=0.73 p=0.5



CHAPTER FOUR

Pain Relief for Neonatal Circumcision – A Systematic Review

During the first few days of life, otherwise healthy male infants may be circumcised, frequently without the benefit of effective pain management [8-10]. Because it is a painful elective surgery, performing circumcision without anesthesia causes systemic stress responses including increased output of adrenal corticoids [1], increased heart rate, respiratory rate and decreased arterial oxygen [2], and skin flushing, vomiting and cyanosis. [3] Negative behavioral responses such as changes in sleep/wake state, increased crying [1] and diminished responsiveness to caregivers [4] also occur after circumcision.

The circumcision policy statements of the Canadian Pediatric Society[5], the American Academy of Pediatrics [6], and the American College of Obstetricians and Gynecologists [7], all identify pain and its complications as potentially damaging to infant and child development. Many strategies and techniques for relieving the pain of circumcision surgery have been investigated, including drugs and comfort measures. Pharmacologic preparations have been the most widely studied and are the most commonly used form of pain intervention. Research examining pharmacologic preparations for circumcision pain is the focus of this manuscript.

Anaesthetics or anaesthetic techniques include dorsal penile nerve block (DPNB), ring block (RB) and topical anaesthetics. DPNB for neonatal circumcision was first described by Kirya and Werthmann [11] in 1978. While 1% lidocaine is generally used for the block, 0.25% bupivacaine without epinephrine is also recommended [12]. RB, established by subcutaneous circumferential infiltration of 1% lidocaine around the shaft of the penis near the base, was initially suggested as a method for post-circumcision analgesia [13], but has since been evaluated for treatment of pain during circumcision. Topical anaesthetics including eutectic mixture of local anaesthetics (EMLA - a water-based mixture of 2.5% lidocaine and 2.5% prilocaine) and lidocaine cream in a variety of concentrations have been used for neonatal and pediatric pain associated with frequently performed procedures such as heel stick, venipuncture, and circumcision.

Circumcision pain has also been treated by other drugs or preparations alleged to have analgesic properties. For example, practitioner interest in the use sucrose or other sugar solutions alone or in combination with non-nutritive sucking for procedural pain management has recently increased [14]. Sucrose is thought to activate central endogenous pathways, and stimulate release of endorphins from the hypothalamus, resulting in a rapid-onset analgesic effect that lasts for three to five minutes [15, 16]. Sucking during the delivery of oral sucrose administration stimulates orotactile and mechanoreceptor mechanisms [16, 17,] and may provide more effective relief of procedural pain[17-19]. Acetaminophen is the most frequently prescribed non-opioid oral analgesic used to treat mild to moderate pain in pediatric populations [20, 21]. Acetaminophen is safe and effective and can be administered orally or rectally [22].

The effectiveness of each of these interventions for pain during circumcision has been examined in at least one clinical trial, but little research is available that summarizes the evidence about individual interventions or compares these different treatments against each other.

An abridged version of a systematic review conducted to establish the effectiveness and safety of interventions for relief of pain during neonatal circumcision is presented in this manuscript. It concentrates on the results and implications arising from the most frequently measured pain outcomes (heart rate and crying). The complete review is published in the Cochrane Library [24].

Methods

Randomized controlled trials of pain interventions for male neonatal circumcision were included in this review. Table 1 outlines the study selection criteria.

Data Sources

We searched the following electronic databases from their launch date through May 2004: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PubMed, Web of Science, and Dissertation Abstracts. Keywords and Medical Subject Heading (MeSH) terms included infant/newborn, male, circumcision, penile block, sucrose, lidocaine, EMLA, acetaminophen, local anaesthesia, Gomco clamp and pacifiers. The reference lists of all studies located were hand-searched to identify any additional articles. Abstracts of the triennial World Congress on Pain were screened for the years 1993-1999 inclusive. Language restrictions were not imposed.

Data Extraction and Preparation

Two independent reviewers extracted data and rated the methodological quality of the included studies. Extracted data consisted of: interventions, methods, participant demographics and outcomes. Raters assessed the methodological quality of the included studies using four criteria associated with the potential for bias in randomized controlled trials [25]. Results for a single quality criterion, the reviewers' judgment of the adequacy of allocation concealment (blinding of randomization), are reported here (Table 2). Procedures used to ensure allocation concealment were assessed as adequate (A), unclear (B), or inadequate (C), based on the description of methods provided in the study report.

Disagreements between the reviewers in study selection, data extraction results, or quality ratings were resolved by consensus.

The circumcision procedure can be divided into a number of phases commencing with preparation for surgery and ending with the post-surgical recovery period. The phases of the surgical component of circumcision (i.e. excluding the baseline preparation, drug application and post-surgical recovery phases) begin with application of the forceps to the dorsal foreskin of the penis (dorsal or lateral clamping) and end with removal of the surgical clamp (e.g. Mogen or Gomco surgical device). For this review, outcome data for the surgical component phases were the data of interest.

Some authors reported a single numerical outcome for the entire surgical component, while others reported results by phase or step (e.g. dorsal clamp, adhesion lysis, dorsal incision, etc.). For the latter trials, and depending on the outcome measured, an arithmetic mean (e.g. heart rate) or total (e.g. time crying) across the phases of the surgical component was calculated. Variance formulae for these arithmetic means and totals were derived according to the general formula for linear combinations of variance, and a correlation of 0.5 was assumed [26]. Preparation of the data in this way permitted combination and statistical analysis of data across studies of the same intervention.

A number of the trials included in this review either did not report any outcome data, or did not report data in a form that could be combined for meta-analyses [27-42]. Additional information and data were obtained from the authors of three of the papers [28, 32-33]. Where no further information was available, data were either derived from graphs contained in the reports, [27-30, 36-38, 43] calculated from other summary statistics, or, in the case of missing variances, imputed using a method described by Follman [26].

Data Analysis

Data from individual trials were pooled when appropriate and analyzed using the fixed effects model in the statistical package RevMan 4.2 provided by the Cochrane Collaboration. The weighted mean difference (WMD) with 95% confidence intervals was calculated as the summary statistic when the data were reported in units that were compatible between studies. When the units were not compatible, the standardized mean difference (SMD) was calculated and used to derive an estimate of the WMD following a method described in detail in the full review [24]. Heterogeneity was assessed quantitatively with the I-squared (I^2) statistic which indicates the percent of between study variability [44]. Non-zero results are reported here. An I^2 greater than 50% is considered large and was assumed to reflect substantial inter-study heterogeneity.

Results

Description of the Studies

The search of the electronic databases identified 210 unique references. Two reviewers independently scanned all 210 references to determine if they met the review criteria. Of the 210, the full texts of forty-two reports were evaluated for possible inclusion in this review. Six studies were excluded either because the intervention was not randomized [45-47], the trial had no comparison group [48, 49], or because the trial was not a direct evaluation of interventions for pain relief [50]. Two of the included studies reported different outcome data from the same trial [4, 31]. Two trials were reported as abstracts only [41, 42] and one was a report of an unpublished Masters thesis [51]. Ultimately, thirty-five studies (thirty-six reports) were included in this review. Thirty-three trials enrolled healthy, full term neonates in the first few days of life. Two trials included infants born preterm that were ready for discharge from neonatal intensive care at the time of circumcision [30, 52].

In their trials, the researchers tested a variety of pain interventions. These included penile blocks, topical anaesthetics, oral sucrose, and oral analgesics. Three studies examined nonpharmacologic interventions not commonly used for circumcision pain such as music therapy [32, 34, 35]. A single trial tested a specially designed restraint [53] and two trials evaluated surgical devices (i.e. the Mogen and Gomco clamps) in combination with pharmacologic interventions [54, 55]. Overall, 28 different comparisons were made.

Methodological Quality of the Included Studies

Few authors described procedures for power analyses or sample size calculation, and sample size for the studies was generally small. Of the 35 included studies, 19 were rated A for quality [27, 30-32, 36, 38, 40, 51, 52, 56-65] and 15 were rated B [28, 29, 33, 34-37, 39, 41-43, 53-55, 66, 67]. A single study was rated C for quality [68]. Nine trials used a double blind for all interventions tested [32, 38, 43, 51, 58, 59, 61, 63, 65]. Partial blinding was achieved in some cases through inclusion of a sham or placebo group [27, 29, 31, 33, 54, 60, 67].

The procedures used by researchers in the included studies were varied. For example, within the trials of DPNB differences were found in the length of time fasting prior to circumcision, the anaesthetic dose, the wait time after anaesthetic administration and before the start of surgery, and in the type of surgical device used. In some trials a single practitioner (often the principal investigator) performed all circumcisions [52, 56, 58], in others, a number of operators participated [53, 59, 61]. In some trials, all study subjects received additional non-study interventions that could have affected pain responses, including pacifiers [30, 37, 39, 53, 55, 58, 59], sugar pacifiers [52], DPNB [53] and EMLA [54]. These variations in procedures could have had an impact on individual trial results and consequently may limit the comparability of results across trials of the same intervention.

For this review, pain was the primary outcome of interest. Pain was assessed by physiological, biochemical or behavioral indicators, or by observer-rated pain scales. For the included studies, physiological indicators were heart rate, oxygen saturation, respiratory rate, and blood pressure. Biochemical indices included plasma or salivary cortisol or b-endorphin levels. Duration or percent time crying was the most frequently measured behavioral variable. A variety of observer-rated scales, differing in conceptual development and measurement technique, were also used as proxies for pain. Generally, rationale for choice of outcome indicator was not provided, and only a few authors specified the primary or most pertinent outcome. Because heart rate and cry time were the most frequently measured and reported outcomes, opportunities were best for combining results for these variables across trials of the same intervention. For that reason, the results for these are presented in this manuscript. A complete account of all outcome data and summary estimates for the included studies can be found in the full report [24].

Comparisons of Penile Blocks

Nineteen trials compared DPNB, RB or local block (LB) with saline penile block (a placebo), no treatment, or another active intervention [27, 30, 31, 33, 36, 39, 40, 52, 53, 55-57, 59, 60, 62, 64, 66-68]. Paired comparisons are discussed in the following sections.

Penile block versus no treatment or placebo. Fourteen trials involving 592 infants compared DPNB to no treatment or placebo [27, 30, 31, 33, 36, 39, 40, 55, 57, 60, 64, 66, 67, 68]. Of these, ten authors reported usable heart rate or cry data [27, 30, 33, 36, 55, 57, 60, 66, 67, 68]. Summary effect estimates demonstrated that heart rate in beats per minute (bpm) [WMB -35 bpm, 95% CI -41 to -30; $I^2 = 73\%$; $p < 0.00001$] and percent time crying [WMD -54%, 95% CI -64 to -44; $p < 0.00001$] were lower for neonates that received DPNB compared to placebo or no treatment.

A reduction in percent time crying was found in two trials [56, 60] involving 65 infants that compared RB to placebo or no treatment [WMD -27 %, 95% CI -38 to -15; $I^2 = 68\%$; $p < 0.00001$]. In a single trial [60] the heart rate was lower in the ring block group compared to placebo [MD -29 bpm, 95% CI -52 to -7; $p = 0.02$].

DPNB versus RB. A single trial (27 infants) compared DPNB with RB. Differences in heart rate and crying time (means calculated as described for all surgical phases of the circumcision procedure) were not statistically significant [60].

Penile blocks versus EMLA. Three trials (total of 139 participants) compared DPNB to EMLA [52, 59, 60]. Heart rate was lower for the DPNB group [WMD -17 bpm, 95% CI -23 to -11; $p < 0.00001$]. Heterogeneity in the three trials was large ($I^2 = 93\%$) and may be related to differences in the study populations that included healthy term infants in two trials [59, 60] and hospitalized preterm infants ready for discharge in one [52]. The difference in time crying between the DPNB and EMLA groups measured in one trial [60] involving 29 infants was not statistically significant.

In a single trial of 28 infants, RB was compared with EMLA [60]. Results for heart rate and cry time were not statistically significant.

Penile block versus sucrose. Two trials (127 infants) compared DPNB to sucrose [33, 57]. Time crying [33] [MD 166 sec, 95% CI -211 to -121; $p < 0.00001$] measured in one trial and heart rate measured in both [WMD -27 bpm, 95% CI -33 to -20; $I^2 = 94\%$; $p < 0.00001$] were lower in the DPNB group. Differences between the trials in the dose (2 versus 10 ml) and delivery method (oral syringe versus nipple) of the sugar solution may account for the large heterogeneity.

Adverse effects. Localized bleeding and hematoma at the puncture site are the most commonly reported adverse effects associated with DPNB [69-71]. Overall, for the trials included in the review, reports of adverse effects with DPNB were infrequent and were limited to emesis, [27] minor post-surgical bleeding, [27, 62, 64, 67] hematoma, penile edema, [52] and swelling [64].

Comparisons of Topical Anaesthetics

Topical anesthetics versus placebo. Six trials (200 subjects) compared EMLA to placebo [28, 32, 41, 43, 60, 65]. Both heart rate [WMD 15 bpm, 95% CI -19 to -10; $p < 0.00001$] and percent time crying [WMD 16%, 95% CI -21 to -7; $p < 0.00001$] were lower in the EMLA group.

Another comparison carried out in three trials (115 neonates) was for lidocaine cream versus placebo [38, 63, 65]. The concentration of lidocaine varied between the trials from 4% to 30%. Data from two trials [38, 65] demonstrated that heart rate [WMD -9 bpm, 95% CI -14 to -4; $p = 0.0004$] and cry time [WMD -60 seconds, 95% CI -99 to -20; $p = 0.003$] were lower in the lidocaine group compared to placebo.

EMLA versus 30% lidocaine cream. In a single study involving 40 patients, EMLA was compared with 30% lidocaine cream [65]. Heart rate was lower in the EMLA group [MD -12 bpm, 95% CI -19 to -4; $p = 0.002$], but the difference in time crying was not statistically significant.

EMLA versus other interventions. In two trials involving 67 infants [37, 41] EMLA cream was compared with sucrose. No significant differences were found between the groups in heart rate or cry time. In a small pilot study, no significant differences in heart rate and time crying were demonstrated between the EMLA and music therapy groups [32].

Adverse effects. The use of EMLA has been reported to cause local skin reactions such as blanching, erythema, and edema at the site of application. These effects are usually transient and are generally not considered to be serious [72]. For the trials included in this review, adverse effects were reported with the use of EMLA and included erythema [52], and minor foreskin pallor and edema [43]. In one trial significant redness and blistering of the foreskin forced closure of the EMLA arm of the study [30] and data related to these patients was not analyzed.

A serious but relatively rare risk associated with EMLA use in neonates is methemoglobinemia (MetHb). A recent systematic review of the use of EMLA for acute procedural pain demonstrated that the risk of significant MetHb (defined as MetHb > 5% and clinical signs such as cyanosis requiring treatment) is low with single dose applications [73]. Two trials of EMLA included in this review evaluated MetHb levels [43, 60] and found them to be within normal limits.

Comparisons of Oral Sucrose

Oral sucrose versus placebo or no treatment. A variety of concentrations (24 to 50%) and volumes (1.5 to 10ml) were tested in eight trials involving 360 infants that compared sugar solutions to placebo or no treatment [29, 33, 41, 42 51, 53, 54, 57]. Results for the five trials that reported useable heart rate or cry data [29, 33, 41, 51, 57] were not statistically significant, and individual trial results were inconsistent in direction. Differences between trials in the dose of sucrose solution provided (due to variability in the volume and concentration) and in the method of delivery may account for the inconsistent results. In five trials the sucrose solution was dispensed via a nipple [29, 42, 53, 54, 57], in two the sugar solution was given via oral syringe [33, 51], and in one the method of delivery was not specified [41].

Adverse Effects. Reports of adverse effects associated with sucrose administration are rare. Gagging with oral sucrose by oral syringe was reported in one trial [51].

Comparisons of Oral Analgesics

Oral analgesics versus placebo. Two trials involving 104 infants compared oral acetaminophen to placebo [58, 61]. Results for heart rate and crying were not statistically significant between the groups. There were no adverse effects reported with the use of acetaminophen.

Comment

Circumcision is a painful procedure that is not recommended as a routine practice for healthy male newborns. It must be emphasized that none of the interventions examined in these trials completely eliminated the pain responses associated with this elective procedure.

If circumcision is performed, DPNB, RB and the topical anaesthetics EMLA and lidocaine cream can be recommended over no treatment for pain management during the procedure. DPNB is consistently superior to placebo, no treatment, EMLA or sucrose in demonstrating statistically and clinically significant reductions in the pain outcomes of heart rate and time crying. Although it has not been extensively evaluated, RB is also effective compared to placebo and may be easier and safer to administer because it avoids the risk of injection of the anaesthetic medication (usually 1% lidocaine without epinephrine) into the dorsal vessels [56]. Oral sucrose and oral analgesics are not effective and are not recommended for treatment of the pain associated with acute tissue injury during the procedure.

In addition, both EMLA and lidocaine cream are superior to placebo for reducing pain during circumcision. However, the clinical utility of these topical anaesthetics for circumcision may be limited because they are difficult to apply and because of the lengthy time (60-90 minutes) required to achieve maximum anaesthetic effect.

This review incorporates data from 35 trials that examined a variety of pain interventions for circumcision and the results are generally applicable to current practice. However, a number of limitations in the primary studies were identified and therefore the results should be viewed with some caution. Sample size was generally small among the trials. And, although all trials were described as randomized, 15 out 35 did not provide adequate information for assurance of allocation concealment, a key factor in preventing systematic bias. In some of the trials, the interventions could not be masked, and only nine trials used a double-blind for all interventions. Lack of blinding is also a potential source of bias in a number of the trials.

It was difficult to assess the similarity among trials as to what steps or phases constituted the circumcision procedure and exact methods for outcome data collection were not always clearly described. Differences in the steps of the circumcision procedure could affect the comparability of the outcome results across studies. For this review, we assumed that the steps were essentially equivalent for all of the trials and prepared and analyzed the data accordingly although in many cases not enough information was provided to be certain of this. We analyzed mean pain for the entire circumcision procedure, rather than for various phases of it. It is possible that different conclusions would be drawn had we been able to evaluate the efficacy of the interventions for comparable steps or phases of the circumcision across all trials.

Pain associated with the injection of penile blocks has been a concern for practitioners, and may influence routine use of this intervention despite its effectiveness [67]. In one study [60], data for topical anaesthetic groups were combined for comparison with penile block groups to assess pain responses during drug administration. Heart rate increased for both groups during drug administration and was greatest for the penile block groups, but time crying during drug administration was not significantly different between the groups. Newborns in the penile block groups stopped crying 92 seconds after drug administration compared with 63 seconds for the topical groups. Three other studies included in this review [27, 31, 67] compared both saline DPNB (sham treatment) and no treatment arms in an attempt to control for the effects of pain associated with the injection and fluid volume compression on penile sensation. None of the researchers found statistical differences between outcomes for the sham treatment and no treatment arms. We found no evidence to indicate that the pain associated with block injections offsets the benefits of block anaesthesia, and use of penile blocks should not be avoided for this reason.

Another factor that may influence routine use of penile blocks is the "wait time" required after administration for adequate anaesthesia. The waiting period is a concern for clinicians because it increases the total time required to complete the circumcision. One trial included in this review compared different waiting times after anaesthetic administration for two different anaesthetics (lidocaine and chloroprocaine) [29]. The authors found that chloroprocaine was as effective as lidocaine for penile blocks, with a more rapid onset of anaesthesia. In other trials, wait times of three [56,57], four [40, 59, 68], and five minutes [30, 31, 36, 53, 55, 66, 67] were used, usually without rationale for the choice. In order to achieve maximum effectiveness a wait time of five minutes after penile block administration and before the start of surgery is recommended [23] and we found no evidence that conflicted with this recommendation.

The results of a previous although limited systematic review are consistent with our finding that DPNB is the most effective pain intervention[22]. That review differs from this one in that it included data from weaker quasi-randomized trials, combined few outcomes using meta-analysis and did not fully exploit synthesis of existing data. For example, the authors were only able to combine time crying and oxygen saturation data from two trials of DPNB versus placebo using meta-analytic techniques.

The current review expands the quantitative synthesis of outcome data from thirty-five trials, thus increasing the power of the statistical analysis and the number of comparisons. Outcome data from trials of lidocaine cream, oral sucrose and acetaminophen were combined, allowing us to go beyond the conclusions of the previous review to state that sucrose and acetaminophen are not effective interventions for pain during circumcision.

Implications for Research

Future pain research should compare active interventions with proven effectiveness for circumcision pain; a placebo or no treatment control group is no longer ethically acceptable. Because it was the most effective of the interventions tested, the influence of different "wait times" after anaesthetic administration and before the start of the circumcision on penile block effectiveness, and the relative ease of administration of DPNB versus RB should be investigated. In addition, the rationale for the choice of pain outcomes should be provided, and thresholds for clinical as well as statistical significance of outcome results should be determined a priori.

Circumcision is generally regarded as a straightforward procedure from which a healthy neonate quickly recovers. As a result, interventions are directed primarily at management of pain during the time it takes to complete the surgery. However, recent research has demonstrated that neonates exhibit hyper-alertness and immobility after circumcision, indicating that they experience significant pain and distress in the post-circumcision period [73]. Although the post-surgical phases of circumcision were not the focus of this review, it is possible that several of the study interventions could be effective outside of the period of acute tissue injury. For example, although not effective during circumcision, oral acetaminophen did appear to provide some pain relief in the post-operative period in one trial [61]. The use of it and other interventions as adjuncts following appropriate pain management during circumcision should be investigated further. In addition, research should be conducted to clarify effectiveness and to determine an optimal dose and delivery method for oral sucrose during and after commonly performed procedures.

As mentioned, many of the 35 trials included in this review did not report outcome data that was suitable for synthesis using meta-analytic techniques. And, although all of the trials were described as randomized, fifteen reports did not provide enough information about procedures to confirm satisfactory allocation concealment.

Other reports provided inadequate or ambiguous information about sample size and how subject loss through attrition after randomization affected data analysis [27–29, 32, 34, 41, 42, 62]. Inadequate reporting of this nature brings the quality of these trials into question (perhaps unfairly), frustrates synthesis efforts, and impedes development of recommendations for evidence-based practice. As a remedy to this situation, the CONSORT group has provided a 22 item checklist and flow diagram [75] intended to help authors improve reporting about the results of parallel-group randomized trials. Consistent use of these tools will ensure that readers are provided with information essential to judging the validity of trial results, and will also facilitate future synthesis research.

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Table 1. Selection criteria for studies of pain relief for male neonatal circumcision

Category	**Criteria**
study population	male term or preterm newborns, undergoing circumcision in the neonatal period, with postnatal age maximum 28 days after reaching 40 weeks corrected gestational age
study type	randomized controlled trials
study interventions	interventions to relieve circumcision pain whether compared with placebo, no treatment, or another active intervention
study outcomes	pain as assessed by physiological, biochemical, cry variables, or by composite pain or behavioral scales or scores; complications of pain interventions were assessed as secondary outcomes.

Table 2. Characteristics of the Included Studies

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Trials of penile blocks				
Arnett et al, 1990	52 fullterm newborns	0.4 ml 1% lidocaine DPNB 0.4 ml saline DPNB no treatment	heart rate ^{g} oxygen saturation ^{g} irritability score ^{m,SD} adverse effects	adequate
Butler-O'Hara et al, 1998	50 preterm newborns	0.5 ml LP cream 0.7 – 1.0 ml 1% lidocaine DPNB + placebo cream	heart rate ^{m,SD} *pain score ^{m,SD} adverse effects	adequate
Dixon et al, 1984; Holve et al, 1983	31 fullterm newborns	0.8 ml 1% lidocaine DPNB 0.8 ml saline DPNB no treatment	no useable data adverse effects	adequate
Hardwick-Smith et al, 1998	40 fullterm newborns	1.0 ml 0.5% lidocaine ring block) no treatment	time crying ^{m,SD} oxygen saturation ^{m,SD} respiratory rate ^{m,SD}	adequate
Herschel et al, 1998	120 fullterm newborns	0.8 ml 1% lidocaine DPNB 10 ml 50% sucrose no treatment (n=40)	heart rate ^{m,SD} oxygen saturation ^{m,SD}	adequate

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Holliday et al, 1999	50 preterm, low birthweight newborns	0.8 ml 1% lidocaine DPNB + placebo cream) LP cream (arm stopped, excluded from analyses) placebo cream	heart rate ^{g} oxygen saturation ^{g} respiratory rate ^{g} systolic blood pressure ^{g} behavioral score ^{g} serum *B*-endorphin ^{m,SD} adverse effects	adequate
Howard et al, 1999	62 fullterm newborns	1g LP cream + 0.8 ml saline DPNB 0.8 ml 1% lidocaine DPNB + 1g placebo cream	heart rate ^{m,SE} respiratory rate ^{m,SE} distress scale ^{m,SE}	adequate
Kass et al, 2001	71 fullterm newborns	lidocaine DPNB 2 ml 50% sucrose 2 ml water	heart rate ^{m,SD} *time crying ^{m,SD} oxygen saturation ^{m,SD} pain scale ^{m,SD}	unclear
Kurtis et al, 1999	48 fullterm newborns	0.8 ml 1% lidocaine DPNB, Mogen clamp no treatment, Mogen clamp 0.8 ml 1% lidocaine DPNB, Gomco clamp no treatment, Gomco clamp	heart rate ^{m,SD} time crying ^{m,SD} oxygen saturation ^{m,SD} respiratory rate ^{m,SD} salivary cortisol ^{m,SD}	unclear

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Lander et al, 1997	54 fullterm newborns	0.8 ml 1% lidocaine DPNB 0.8 ml 1% lidocaine ring block 2g LP cream placebo cream	*heart rate ^{m,SD} time crying ^{m,SD} adverse effects	adequate
Masciello, 1990	30 fullterm newborns	0.8 ml 1% lidocaine DPNB 0.8 ml 1% lidocaine local block no treatment	plasma cortisol ^{m,SD}	unclear
Maxwell et al, 1987	30 fullterm newborns	0.8 ml 1% lidocaine DPNB no treatment control	heart rate ^{g} oxygen saturation ^{g} systolic blood pressure ^{g}	adequate
Newton et al, 1999	194 fullterm newborns	0.8 ml 1% lidocaine DPNB 0.8 ml 1% buffered lidocaine	adverse effects	adequate
Spencer et al, 1992	75 fullterm newborns	lidocaine DPNB – 5 min WT lidocaine DPNB – 2 min WT 1% chloroprocaine DPNB – 3 min WT 1% chloroprocaine DPNB – 5 min WT no treatment control	no useable data	unclear
Stang et al, 1988	60 fullterm newborns	0.8 ml 1% lidocaine DPNB saline DPNB no treatment control	time crying $^{m, SE}$ plasma cortisol $^{m, SE}$ adverse effects	unclear

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Stang et al, 1997	80 fullterm infants	0.8 ml 1% lidocaine DPNB, padded restraint, water 0.8 ml 1% lidocaine DPNB, regular restraint, 24% sucrose 0.8 ml 1% buffered lidocaine DPNB, regular restraint, water 0.8 ml 1% lidocaine DPNB, regular restraint, water	distress scale $^{m, SD}$ plasma cortisol $^{m, SD}$	unclear
Williamson et al, 1983	30 fullterm newborns	0.6 – 0.8 ml 1% lidocaine DPNB no treatment	heart rate $^{m, SD}$ time crying $^{m, SD}$ tcpO^{2} $^{m, SD}$	inadequate
Williamson et al, 1986	30 fullterm newborns	lidocaine DPNB no treatment	plasma cortisol $^{m, SE}$	adequate
Williamson, 1997	30 fullterm newborns	lidocaine DPNB no treatment	adverse effects	adequate
Trials of topical anesthetics				
Benini et al, 1993	28 fullterm newborns	0.5 ml LP cream 0.5 ml petroleum jelly	heart rate $^{m, SD}$ time crying ^{g} oxygen saturation $^{m, SD}$ facial action score $^{m, SD}$	unclear

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Joyce et al, 2001	23 fullterm newborns	1 -2g LP cream + music 1 -2g LP cream placebo cream + music placebo cream	heart rate $^{m, SD}$ cry duration $^{m, SD}$ oxygen saturation $^{m, SD}$ respiratory rate $^{m, SD}$	adequate
Mohan et al, 1998	60 fullterm newborns	5g 5% LP cream + 2 ml 24% sucrose 5g 5% LP cream + water 2 ml 24% sucrose	heart rate ^{g} oxygen saturation ^{g} blood pressure ^{g}	unclear
Mudge et al, 1989	44 fullterm newborns	4% lidocaine cream placebo cream	heart rate ^{g} time crying ^{g} oxygen saturation ^{g} respiratory rate ^{g}	adequate
Taddio et al, 1997	68 fullterm newborns	1g LP cream 1g placebo cream	heart rate $^{m, SD}$ time crying $^{m, SD}$ *facial action score ^{g} blood pressure $^{m, SD}$ adverse effects	unclear
Weatherstone et al, 1993	30 fullterm newborns	0.5g 30% lidocaine cream placebo cream	behavioral score serum b-endorphin $^{m, SD}$	adequate
Woodman, 1999	61 fullterm newborns	5% LP cream 30% lidocaine cream placebo cream	heart rate $^{m, SD}$ time crying $^{m, SD}$ oxygen saturation $^{m, SD}$	adequate

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Zahorodny et al, 1998	53 fullterm newborns	1g 5% LP cream + 2ml 50% sucrose 1g 5% LP cream + 2 ml water 1g placebo cream + 2 ml water 1g placebo cream + 2 ml 50% sucrose	time crying $^{\%}$	unclear
Trials of oral sucrose				
Blass et al, 1991	30 fullterm newborns	1.5 ml 24% sucrose 1.5 ml water no treatment	time crying ^{g}	unclear
Kaufman et al, 2002	57 fullterm newborns	24% sucrose + Mogen clamp 24% sucrose + Gomco clamp water + Mogen clamp water + Gomco	no useable data	unclear
Zahorodny et al, 1999	61 fullterm newborns	10 ml 50% sucrose 10 ml water no treatment	no useable data	unclear
Zolnoski, 1993	20 fullterm newborns	2.4 ml 24% sucrose 2.4 ml water	heart rate $^{m, SD}$ time crying $^{m, SD}$ adverse effects	adequate

Study	Participants # randomized	Interventions/ Comparisons	Outcome Data Reported	Allocation Concealment
Trials of oral analgesics				
Howard et al, 1994	44 fullterm newborns	acetaminophen 15mg/kg/dose (n=23) placebo (n=21) 2 hr prior; q6h for 24 h post	heart rate $^{m, SD}$ time crying $^{m, SD}$ respiratory rate $^{m, SD}$ comfort score $^{m, SD}$	adequate
Macke, 2001	60 fullterm newborns	acetaminophen 10mg/kg (n=29) placebo (n=31) 1 h prior	heart rate $^{m, SD}$ time crying $^{m, SD}$ feeding scale $^{m, SD}$	adequate
Trials of other interventions				
Marchette et al, 1989	103 fullterm newborns	classical music (n=25) intrauterine sounds (n=15) no treatment (n=18)	no useable data	unclear
Marchette et al, 1991	121 fullterm newborns	taped music (n=20) intrauterine sounds (n=20) pacifier (n=20) music and pacifier (n=20) intrauterine sounds and pacifier (n=20) no treatment (n=20)	no useable data	unclear
Total = 35 trials	2000 randomized			

*** primary outcome identified; g = graph; m, SD = mean, std deviation; SE = std error**

CHAPTER FIVE

General Discussion and Conclusions

Three objectives guided the research described in this thesis: to assess the usefulness of research synthesis for advancing nursing knowledge; to conduct a systematic review to assess the effectiveness and safety of interventions for relief of pain during circumcision; and, to develop evidence-based recommendations for best practice in circumcision pain management and identify areas where further research is needed.

The foundation for the three objectives is the question about the value of research synthesis for nursing. I carried out a systematic review of the effectiveness and safety of pain relief interventions for neonatal circumcision as a demonstration of the potential contribution of research synthesis for nursing practice and research. As mentioned, male neonatal circumcision was selected as an exemplar for the research because it is an area where nurses play a variety of roles. Nurse practitioners perform circumcision; other nurses are involved in education of parents and the public. To meet their professional responsibilities, nurses require information about best practice, as can be derived from a synthesis of existing research evidence.

Research synthesis has a role to play in the development of nursing knowledge. An influential publication in the early 1980's detailed a comprehensive review of three decades of nursing research and concluded that the investigations were primarily non-cumulative in nature (Brown, Tanner, & Padrick, 1984). The disturbing observation that research was not linked to prior work and did not serve to refine, extend or refute theory, was corroborated in several subsequent reviews (Loomis, 1985; Moody et al., 1988; Murphy & Feston, 1991). Concerns were raised about the need for nurse scientists to proceed in earnest to systematically build a knowledge base for the discipline. Expression of these concerns was followed by calls for a focus on cumulation in the development of nursing knowledge and by discussions about the means to achieve this (Estabrooks, Field, & Morse, 1994; Jensen & Allen, 1996; Kirkevold, 1997).

Research synthesis has since established a foothold in the arsenal of investigative strategies employed by nurse scientists. The rigorous, systematic methods have immense potential to advance knowledge development for nursing in several key areas.

It is important to emphasize that research synthesis methods are not intended to support the integration of knowledge from primary studies conducted in a particular discipline; they are discipline-neutral and question-specific. Synthesis of only the nursing research exploring pain responses during circumcision would not produce valid results if the bulk of the investigations were conducted in other disciplines. Instead, synthesis methods provide a means to determine what the literature in its entirety says about a phenomenon or question of interest. Synthesis offers the additional advantage of comparison of all existing evidence, and this can help to explain why and under what conditions a particular effect occurs.

Synthesis serves as an objective means to determine the state of the science about a phenomenon or research question of interest, while generating several important outcomes. For example, through review of the existing literature gaps in knowledge are identified and this provides direction for future investigations. Awareness of what has gone before helps investigators to avoid redundant research so that resources can be directed to address real knowledge gaps. Careful scrutiny of study reports during the review process reveals deficiencies and achievements in previous study designs and this informs the design of future research.

Evidence-based nursing (EBN) has been defined as "the conscientious, explicit and judicious use of theory-derived, research-based information in making decisions about care delivery to individuals or groups of patients and in consideration of an individual's needs and preferences" (Ingersoll, 2000, p. 152). Research synthesis has a fundamental role to play in the development and refinement of the theory needed to guide evidence-based practice (Estabrooks et al., 1994; Sandelowski, Docherty, & Emden, 1997). Not surprisingly, the products of synthesis have been identified as a critical resource for many clinicians. They often lack the time, access to research information, and the critical appraisal skills necessary for locating and using available evidence to improve their practice. The results of synthesis, available on line through sources such as the Cochrane Library, are valuable tools for nursing to facilitate practice change, or to support the development of recommendations or standards for best practice.

Additionally, the results of synthesis have a logical role to play in the education of nursing students by exposing them to an important component of the existing cumulative disciplinary knowledge base. Through synthesis students are presented with a coherent overview of the empirical evidence relevant in the discipline, and this will help to establish an appreciation of the link between evidence and best practice. Additionally, awareness of real gaps in knowledge can be influential at the graduate level in generating new research questions.

In considering the potential of research synthesis for the development of knowledge, nursing has taken the position that legitimate evidence for practice must be more inclusive than what was originally envisioned by the pioneers of evidence-based medicine. Nursing has clearly stated a preference for merging empirical evidence and theory with clinical expertise, client input, and ethical, personal and aesthetic perspectives to guide practice and decision-making (Gregson, Meal, & Avis, 2002).

Complaints that synthesis methods favor questions that can only be answered by evidence from randomized controlled trials are becoming less frequent as concerted efforts are made to develop methods for synthesis of findings from qualitative and non-RCT research. When used by nurses, these new techniques will support the growth of disciplinary knowledge based on a diversity of evidence (Dixon-Woods, Fitzpatrick, & Roberts, 2001; Popay, Rogers, & Williams, 1998; Upshar, VanDenKerkhof, & Goel, 2001).

Limitations of the Method

Although research synthesis has many advantages for nursing, it also has limitations. These include those related to the quality of primary studies, and the comprehensiveness of the description of methods and results in the primary study reports.

Quality. The conclusions of any systematic review are dependent on the quality of the primary studies that are included in the review. If the 'data' are flawed, the results of the review will be adversely affected or possibly invalid. Consequently, assessment of the quality of primary studies is generally recommended.

In the context of synthesis of quantitative research, quality relates primarily to the internal validity of the primary studies. Internal validity means that the differences between the study groups can be attributed to the effect of the intervention (except for random error), and it is dependent on the extent to which systematic error (bias) is minimized in the study procedures. To date, the bulk of the methodological research about the synthesis of quantitative data has focused on criteria relevant to the design and conduct of randomized controlled trials. Although a variety of checklists and tools are available, consensus has not been reached regarding the best techniques for quality assessment (Moher, Jadad, & Tugwell, 1996).

Comprehensiveness of descriptions of methods. Transparency about research procedures and adequate reporting of outcome data, sample size, and other details is essential for readers to judge the validity and applicability of primary studies for synthesis. Although appropriate research procedures may have been followed, quality can only be judged based on the information contained in the written report. Inadequate reporting can place limitations on the conduct and ultimately on the results of synthesis research. This has been identified as a commonly encountered barrier in research synthesis efforts (Egger, Davey Smith, & Altman, 2001; Popay et al., 1998). As a partial solution to this problem, the CONSORT group has developed a checklist and a flow chart (Moher, Schultz, & Altman, 2001) to assist authors to improve reporting on the conduct and results of quantitative studies, specifically parallel-group randomized trials. These guidelines have been adopted by nurse researchers as a means to improve the communication between the researcher and the research user (Bennett, 2005). Similar initiatives are underway for the reporting of other quantitative research designs and qualitative research (Dixon-Woods, Shaw, Agarwal, & Smith, 2004). Improvements in the reporting of primary research will facilitate accurate quality assessment (once valid criterions are agreed upon) and ensure that the information required to conduct synthesis research is contained in primary reports.

Reporting of data and findings. The findings provided in the reports of the primary studies often present significant analytic challenges. Authors often do not give details of outcome results or do not report the results in a form that can be analyzed using meta-analytic techniques. Measurement techniques can be dissimilar across studies.

The challenges presented by the amount, type and format of quantitative results contained in primary study reports can be addressed using sophisticated data preparation and analysis techniques such as those used for this review which are described in detail in Manuscript Two. These techniques maximize the use of the outcome results and support analysis of the effect of interventions for the associated comparisons. Obviously, it is preferable that complete outcome data be clearly depicted in the primary study report.

Recommendations Arising from the Research

Recommendations for best practice and recommendations for future research evolved from the systematic review (see Appendices B and C). The evidence that supports each of these recommendations is categorized here as substantive, moderately strong, or weak. Evidence can be considered substantive when results are consistent across several studies of the effectiveness of the same intervention. With multiple trials, the number of subjects and data involved increases, and in turn, the power to determine an accurate estimate of effect is increased.

The issue of the substantive nature or amount of evidence should not be confused with what the evidence indicates about the effectiveness of an intervention. For example, the evidence for the effectiveness of dorsal penile nerve block (DPNB) is considered substantive because there are 14 studies showing consistent results indicating the effectiveness of this intervention in reducing pain responses during circumcision. In contrast, the results for ring block (RB) demonstrate a positive effect, but are not considered as substantive as those for DPNB because only two reports of trials involving a small number of subjects that evaluated this intervention were identified.

Based on the systematic review, substantive evidence exists that:

- Circumcision causes severe pain
- None of the pain interventions evaluated in the trials included in this review completely eliminated pain responses during circumcision
- DPNB is the most effective intervention for reducing pain responses during circumcision
- Eutectic mixture of local anaesthetics (EMLA) is effective in reducing pain responses but is less effective than DPNB
- Adverse events from the pain interventions evaluated in the review are rare and not serious.

Moderate evidence exists that:

- RB is effective for circumcision pain
- Circumcision surgery should begin no sooner than 5 minutes after administration of a penile block using 0.8 ml lidocaine without epinephrine
- Circumcision should start no sooner than 60 minutes after EMLA is applied and covered by an occlusive dressing. EMLA should be re-applied if the infant voids during the wait time.

Weak evidence exists for:

- Using the Mogen clamp for circumcision instead of the Gomco clamp to reduce the time it takes to do the surgery and may reduce the total amount of pain experienced.

No evidence exists to support use of:

- Oral sucrose for pain during circumcision
- Oral analgesics (acetaminophen) for pain during circumcision.

Recommendations for Future Research

It is of primary importance that active interventions for circumcision pain are compared with each other in future research; a placebo or no-treatment group is no longer acceptable. To ensure the best possible anaesthesia, the effect of different 'wait times' on the effectiveness of penile blocks should be investigated. The relative ease of administration of DPNB versus RB should be explored to encourage use of the safest and easiest to administer penile block intervention. Finally, there is a need for effective pain management during the post-surgical period and the effectiveness of oral sucrose and oral analgesics for pain management beyond the period of acute tissue injury should be investigated.

Conclusions

The results of my research establish several points. First, this synthesis of the existing research on pain interventions of neonatal circumcision summarizes and integrates the results of 35 individual studies and provides answers about the effectiveness of the pain interventions. The results of the synthesis are relevant for nursing practice and will assist practicing nurses to provide effective pain management and to educate parents of newborns undergoing elective circumcision. Pain assessment and management are critically important practice issues for nursing, especially in working with vulnerable non-verbal populations. Knowledge gained from this synthesis also builds awareness about neonatal pain that may lead to future innovations in nursing practice. Additionally, the results provide nurse researchers (and researchers from other disciplines) with information about the 'next best steps' for investigation of acute procedural pain in neonates. Accordingly, a claim can be made that research synthesis methods are appropriate for nursing.

Second, the state of the science for pain management during neonatal circumcision has been determined. The direction for further investigation has been recommended to determine the best method of delivery for the interventions that are effective for circumcision pain.

Finally, the results of this research make a unique contribution to the knowledge about the effectiveness and safety of interventions for neonatal circumcision because sophisticated data analysis procedures allowed aggregation of outcome data from 28 of the 35 studies included in the review. Athough the Canadian Pediatric Society (1996), and the American Academy of Pediatrics (1999) cite several options for pain management during circumcision, their current position statements on circumcision stop short of recommending best practice, Those position statements and the position statements of the American Medical Association (2005), and the American College of Obstetricians and Gynecologists (2001) can be updated based on the results of this systematic review.

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Appendix A:

Pain relief for neonatal circumcision (Protocol)

Brady-Fryer B, Blankston G, Lander J

THE COCHRANE
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Pain relief for neonatal circumcision (Protocol)

Brady-Fryer B, Blankston G, Lander J

This Review should be cited as:
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BACKGROUND

Elective circumcision of male newborns is commonly performed in the first few days after birth. Approximately 1.2 million newborn males are circumcised in the United States annually at a cost of 150 to 270 million dollars (AAP 1999). Precise Canadian data are not available because the procedure has been delisted in many provinces, but it is estimated that 48% of male neonates born in Canada are circumcised (CPS 1996).

As an invasive, painful procedure, unanesthetized circumcision elicits systemic stress responses in the vulnerable newborn which negatively affect major body systems. Documented physiological and behavioral responses include increased output of adrenal corticoids (Gunnar 1981; Talbert 1976), increased heart rate and respiratory rate, decreased arterial oxygen (Rawlings 1980), skin flushing, vomiting and cyanosis (Poma 1980), changes in sleep/wake state, increased crying (Anders 1974; Gunnar 1981), and diminished responsiveness to parents (Dixon 1984). Unanesthetized circumcision has also been linked with complications such as apnea and choking (Lander 1997), gastric rupture (Connelly 1992), and recurrence of pneumothorax (Auerbach 1978). Infants circumcised without anesthesia exhibit stronger pain responses to routine immunizations during the first six months of life than infants who were not circumcised (Taddio 1997), suggesting that circumcision pain may exert long term effects on infant behavior.

Interventions for circumcision pain

Numerous interventions to prevent or reduce circumcision pain have been examined. These include penile blocks, topical anaesthetics, oral analgesia and sucrose administration, non-nutritive sucking, music and other environmental interventions.

The technique for dorsal penile nerve block (DPNB) was first described in 1978 (Kirya 1978), and it has since been extensively evaluated (Holve 1983; Spencer 1992). More recently, subpubic (Dalens 1989) and penile ring block techniques (Lander 1997) have been examined. Adverse effects of penile blocks appear to be limited to bruising at the injection site (Snellman 1995). Of note, the rapidity of onset of the anesthetic used for the block (generally lidocaine) is intermediate and a "wait time" of five minutes is required to achieve effectiveness (Taddio 2001). Wait time is a concern for clinicians because it increases the total time required for the circumcision surgery; however, inadequate "wait time" influences anesthetic efficacy.

Several types of topical anaesthetics have been evaluated for neonatal circumcision, including eutectic mixture of local anaesthetics (EMLA) and 10 - 30% lidocaine creams. EMLA is a water-based cream that is 2.5% lidocaine and 2.5% prilocaine. Compared with placebo, EMLA attenuates the circumcision pain responses of increased heart rate, facial activity and crying, and decreased oxygen saturation (Lander 1997; Taddio 1997). A meta-analysis of three studies examining this intervention indicates that the use of EMLA results in a significantly lower increase in heart rate (from baseline) and less crying during the various phases of circumcision surgery compared to placebo. In two of the included studies, lower facial action scores suggested less pain in the EMLA treated groups compared to placebo (Taddio 2002).

Potential difficulties with drug administration and the presurgical wait time may limit the feasibility of topical anesthesia as a pain intervention for circumcision in many settings (Lander 1997). Considerable technical skill is required to apply the drug, and to place the occlusive dressing needed to keep it in place. For adequate absorption, EMLA must be applied for at least 60 minutes prior to the surgery (Taddio 1998), and must be reapplied if the infant voids during the wait time.

Methaemoglobinaemia (MetHb), caused by oxidation of hemoglobin by the metabolites of prilocaine, is a serious but relatively rare risk associated with EMLA use in infants less than 12 months of age. A recent systematic review of the use of EMLA for acute pain in infants demonstrated that the risk of significant MetHb is low with single dose applications of 0.5 to 2 g applied for 10 - 180 minutes for fullterm neonates, and 0.5 to 1.25 g applied for 3 - 180 minutes for preterm neonates (Taddio 1998). Local skin reactions, such as blanching, erythema, and edema of the skin, have been reported with the use of EMLA, but these are transient and not considered serious. Evaluation of the frequency of these adverse effects is ongoing.

Sucrose alone or in combination with non-nutritive sucking has been used as a intervention for procedural pain management (Mitchell 2000). Although sucrose in a wide variety of dosages (concentrations from 12 - 24%, and volumes from 0.05 - 2.0 ml) has generally been found to decrease pain responses in neonates (Mitchell 2000; Stevens 1997; Stevens 2002), the optimal dose has not yet been identified. Meta-analyses results indicate that while a 0.24g dose is effective to reduce pain responses in term infants, higher doses do not appear to increase effectiveness (Stevens 1997; Stevens 2002). In comparison, relatively small doses (0.01 - 0.02g) appear to be effective for preterm infants (Johnston 1997). Interest in sucrose as a single or adjunctive intervention for circumcision pain is reflected in the design of recent research (Kass 2001; Kaufman 2002).

Neonatal pain responses

It is difficult to evaluate the effectiveness of interventions for circumcision pain because newborns are non-verbal and display stereotypic responses to a variety of painful and non-painful stimuli. To maximize the validity of pain assessment in newborn populations, three classes of pain indicators or outcomes, biochemical, physiological, and behavioral, are generally employed for research. Salivary and serum cortisol, the most frequently measured biochemical indicators, serve as markers of the stress response to pain because hormones of the hypothalamic-pituitary-adrenal axis are assayed. Physiological indicators include heart rate, respiratory rate, blood pressure, transcutaneous oxygen saturation (TcPO2), transcutaneous carbon dioxide (TcCO2), oxygen saturation (SaO2), palmar sweat, intracranial pressure (ICP) and vagal tone. In newborn populations, heart rate is the most frequently studied physiological indicator. Behavioral indicators include facial expression, cry, gross motor movement, and changes in behavioral state. Facial expression (Grunau 1996) is the most comprehensively studied behavioral indicator of pain.

Multidimensional measurement tools that employ more that one parameter usually contain physiological and behavioral indicators, and occasionally add contextual information to obtain an overall pain score. The Neonatal Infant Pain Scale (NIPS) (Lawrence 1993) and the Premature Infant Pain Profile (PIPP) (Stevens 1996) are multidimensional tools frequently utilized as outcome measures for investigation of acute procedural pain in term and preterm neonates. Although a number of pain measures are available for use with neonatal populations, no single measure has proven to be the best for all situations. Accordingly, all outcomes evaluated in the included studies as measures of neonatal pain will be included in this review.

Summary

The substantial amount of research conducted to date suggests a willingness to address the problem of circumcision pain. However, the majority of neonates are still circumcised without interventions for pain (Myron 1991; Ryan 1994; Snellman 1995; Wellington 1993). This situation persists despite growing awareness that newborns may perceive pain more intensely than older children or adults (Anand 2001; Fitzgerald 1993) and can be significantly compromised by it.

It has been suggested that training to manage circumcision pain is inadequate to promote consistent use of available interventions (Howard 1998). Recent surveys indicate that significant numbers of obstetricians (75%), family practitioners (44%), and pediatricians (29%) do not use analgesia/anesthesia for circumcision because of concerns about adverse drug effects or because they believe that the procedure does not require pain management (Maxwell 1999; Stang 1991; Stang 1998).

Although a wide variety of interventions for circumcision pain have been examined, the individual and relative effectiveness of each has not been systematically assessed. Thus, the apparent reluctance of practitioners to adopt the regular use of pain interventions for circumcision may reflect beliefs that the findings of research conducted to date are collectively un-interpretable. At the same time, negative perceptions of the technical and practical difficulties associated with pain interventions may diminish clinician motivation to implement their regular use.

A systematic review of the research in this area is needed to summarize and identify implications arising from the existing evidence, to provide an informed basis for practice and to identify gaps in knowledge which require further investigation. This review will add to knowledge gained from previous systematic reviews which examined the efficacy of single interventions for circumcision pain (Stevens 2002; Taddio 2002) by evaluating the efficacy and safety of all interventions for neonatal circumcision pain.

OBJECTIVES

To determine the safety and efficacy of interventions to relieve pain associated with neonatal circumcision.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs)

Types of participants

Male term or preterm neonates undergoing circumcision during the neonatal period (with postnatal age maximum of 28 days after reaching 40 weeks corrected gestational age).

Types of intervention

Any intervention intended to relieve pain during the circumcision procedure, for example, penile blocks, topical anaesthetics, oral sucrose administration, oral analgesics, surgical devices or techniques, or environmental manipulation such as music therapy or special restraints. This review will consider trials of interventions for circumcision pain, in which any intervention is compared with placebo, no treatment, or with another active intervention.

Types of outcome measures

The primary outcome will be pain as assessed by:

1. Physiological variables, such as heart rate (HR), respiratory rate (RR), oxygen saturation, or blood pressure (whether reported as change in, mean or absolute values)
2. Biochemical variables, such as salivary or serum cortisol levels (whether reported as pre- and post- measures or as change from baseline values)
3. Cry variables, for example, latency and duration of first cry, total cry duration, and/or percentage of time crying during the circumcision procedure

Each physiological or cry variable will be treated as a separate outcome measure for analysis.

4. Validated pain measures, for example:

- Neonatal Infant Pain Score (Lawrence 1993);
- Neonatal Facial Action Coding System (Grunau 1996);
- Premature Infant Pain Profile (Stevens 1996);
- other pain measures.

Secondary outcomes:

Complications of pain interventions will be assessed as secondary outcomes. These outcomes will include but are not limited to:

1) occurrence/incidence of methaemoglobinaemia (topical anesthesia)
2) blanching and local skin irritations (topical anesthesia)
3) bleeding, bruising and hematoma formation (penile blocks)
4) behavioral responses such a choking, spitting up, etc. during circumcision (all interventions)

Difficulties encountered in implementation of pain interventions, as reported by researchers, will be noted.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

Standard methods as per the guidelines of the Cochrane Neonatal Review Group (CNRG) will be utilized. Detailed search strategies will be developed for each database used to identify studies for inclusion in this review. Studies which are reported only as Abstracts will be included if relevant. The following strategy has been developed for searching MEDLINE, and will be revised appropriately for each additional database used:

1. CIRCUMCISION/exp
2. circumcision surgery.mp
3. newborn circumcision.mp
4. 1 OR 2 OR 3
5. local anaesthes*
6. penile block.mp/exp
7. dorsal penile nerve block.mp/exp
8. ring block.mp/exp
9. 5 OR 6 OR 7 OR 8
10. eutectic mixture of local anesthetics.mp/exp
11. EMLA.mp/exp
12. LIDOCAINE.mp/exp
13. 10 OR 11 OR 12
14. acetaminophen.mp/ OR paracetamol.mp/exp
15. sucrose.mp
16. pacifiers.mp
17. music therapy.mp
18. Gomco clamp.mp
19. Mogen clamp.mp
20. 9 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 4 AND 20
22. HUMAN
23. MALE
24. 22 and 23
25. infant, newborn
26. neonat*
27. 25 OR 26
28. 24 AND 27
29. 21 AND 28
30. clinical trial
31. 29 AND 30

Databases to be searched include: The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2002); MEDLINE 1966 - Dec 2002; EMBASE 1988 - 2002 week 51; CINAHL 1982 - Nov, week 5 2002; PubMed 1966 - Dec 2002; Web of Science 1975 - Dec 2002; Dissertation Abstracts 1986 - Dec 2002; SIGLE 1976 - present. Abstracts of the World Congress on Pain will be searched for the years 1987 - 2002 inclusive. Reference lists of all relevant review articles and all studies identified for inclusion in the systematic review will be screened to identify any additional studies. No language restrictions will be applied.

METHODS OF THE REVIEW

Study Selection

The titles and abstracts (when available) of all reports identified through the electronic search will be scanned independently by two reviewers (BBF, DB). For studies which appear to meet the inclusion criteria, or for those for which there is insufficient data in the title and the abstract to make a decision, the full report of the study will be obtained. Full study reports will be assessed independently by two reviewers (BBF, DB) to establish whether the studies meet the inclusion criteria. Disagreements will be resolved by consensus. A third reviewer will be consulted in situations where resolution of disagreement between the two primary reviewers is not possible. Studies rejected at this stage will be listed in the table of excluded studies, and reasons for exclusion will be recorded.

Quality Assessment

Assessment of the quality of all included studies will be undertaken independently by two reviewers as a component of the data extraction process. Quality criteria to be examined will include: 1) randomisation procedure, 2) allocation of concealment / blinding of randomisation, 3) blinding of intervention, 4) attrition (number of withdrawals and reasons for withdrawal will be recorded), and 5) blinding of outcome measurement. As per the CNRG guidelines, an overall quality score will not be assigned to included studies, but quality of the individual studies will be considered as is appropriate for sensitivity analyses.

Data Extraction

Data will be extracted from included studies by two independent reviewers (BBF, DB) using data extraction forms designed specifically for this review. The data extraction forms will be developed in a draft format and piloted on several studies and modified as required before use. When necessary, additional information and clarification of published data will be sought from individual trial's authors.

The following data will be recorded for each included study:

- year of publication, country of origin, language used, sponsorship, author's name(s) and title of the study;
- study characteristics including setting, design, total sample size;
- details about the study participants including demographic characteristics, and criteria for inclusion/exclusion, description of withdrawals and drop-outs;
- details on the study groups and type of intervention(s) employed and comparisons conducted; and
- details on the exact definitions of outcomes reported, including method of assessment (where pain measures are used, it will be noted whether the measures have been validated),
- any adverse events reported.

Data Analysis

Data will be analysed using the standard statistical methods of the CNRG. If at least two studies that evaluate the same intervention using the same outcome measures are found, data pooling may be attempted. Studies which compare an active intervention with placebo will be analysed separately from those that compare the same active intervention with no treatment. For example: DPNB (active treatment) vs no treatment = comparison 1; DPNB (active treatment) vs saline block (placebo) = comparison 2; DPNB (active treatment) vs RB (active treatment) = comparison 3; DPNB (active treatment) vs sucrose (active treatment) = comparison 4, and so on.

Heterogeneity tests using the Chi-square test with $p < 0.05$ considered statistically significant will be performed to aid in assessing the appropriateness of pooling the data. Clinical heterogeneity will be assessed by examining differences in study quality, participants, interventions and definition or measurement of outcomes of each study. If the data are too heterogeneous to proceed with statistical aggregation, a narrative qualitative summary will be prepared.

Continuous data will be analysed using a fixed effects model for weighted mean difference (WMD) to obtain an overall estimate of effect size. For categorical data the relative risk (RR), risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals will be calculated.

Subgroup analyses

If possible, the following subgroup analyses will be performed:

1) For penile block interventions, subgroup analyses will be conducted to examine the effect size by reported "wait times" from anesthesia administration to start of the circumcision procedure. Studies using the same block technique, dose and type of local anesthetic will be grouped in three categories: no wait time reported, wait time </= 5 minutes, wait time >/= 5 minutes.

2) For sucrose administration interventions, subgroup analyses will be conducted to examine the effect size by dose of sucrose administered. Studies will be grouped according to dose of sucrose (calculated using concentration and volume) administered in two categories: <0.24 g and >/= 0.24 g

POTENTIAL CONFLICT OF INTEREST

none

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Capital Health Authority CANADA
- Faculty of Nursing, University of Alberta CANADA

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COVER SHEET

Title	Pain relief for neonatal circumcision
Reviewers	Brady-Fryer B, Blankston G, Lander J
Contribution of reviewer(s)	Information not supplied by reviewer
Issue protocol first published	2003/1
Review first published	/
Date of most recent amendment	11 May 2004
Date of most recent SUBSTANTIVE amendment	14 July 2002
Most recent changes	Information not supplied by reviewer
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
Date reviewers' conclusions section amended	Information not supplied by reviewer
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Cochrane Library number	CD004217
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Appendix B: Recommendations for Best Practice for Male Neonatal Circumcision

- Neonates should not be circumcised without effective pain management.
- Inform parents requesting circumcision for their male newborn that none of the interventions that demonstrate effectiveness for reducing pain responses during circumcision completely eliminate pain.
- Inform parents that adverse effects from the pain interventions evaluated in this review are rare and not considered serious.
- DPNB using 0.8 ml lidocaine without epinephrine is recommended as the most effective intervention for management of pain during male neonatal circumcision.
- RB using 0.8 ml lidocaine without epinephrine is effective for management of pain during circumcision, but has been less well studied than DPNB. RB may be safer to administer than DPNB because it eliminates the risk of injection of lidocaine into the dorsal vessels.
- A “wait time” of five minutes following administration of a penile block before commencement the circumcision surgery is recommended to ensure maximum anesthetic effect.
- Topical anesthetic preparations containing 5% prilocaine-lidocaine (EMLA) are effective to reduce pain responses during circumcision, but are not as effective as DPNB.
- EMLA (1 - 2 g) should be applied at least 60 minutes prior to the circumcision surgery, covered with an occlusive dressing, and re-applied if the infant voids during the application ‘wait time’.

- Oral sucrose preparations and oral analgesics (acetaminophen) are not effective to reduce pain responses during circumcision and are not recommended for this use.
- Circumcisions performed using the Mogen clamp take less time than is required for the Gomco clamp. A shorter time required for the surgery may reduce the total amount of pain experienced.

Appendix C: Recommendations for Future Research

- Active interventions for circumcision pain should be compared with each other in future research; a placebo or no-treatment group is no longer acceptable.
- The effect of different ‘wait times’ on the effectiveness of penile blocks should be investigated to determine the optimal ‘wait time’ for anesthetic effectiveness.
- The relative ease of administration of DPNB versus RB should be explored to promote patient safety and to encourage use of the safest and easiest to administer penile block intervention.
- The effectiveness of oral sucrose and oral analgesics for pain management beyond the period of acute tissue injury during the circumcision surgery should be investigated.